Drug resistance challenges of the flu pandemic

On June 11, the World Health Organization raised the pandemic level for H1N1 to Phase 6, or global pandemic, with more than 70 countries reporting cases. By late November, the WHO confirmed ~622,500 international cases of H1N1 and over 8,700 deaths in 207 countries and territories. Countries are no longer required to test and report individual cases; therefore, this number represents an underestimation of actual cases. The United States and Canada have been hit the hardest by the pandemic, with over 1,800 deaths reported in the U.S. since the first case was confirmed by the Centers for Disease Control and Prevention on April 15. Much of Central and South America has been heavily impacted as well, and the Americas account for about two-thirds of total H1N1 deaths worldwide. Out of all WHO regions, H1N1 has had the least registered impact on Africa, which has recorded just 104 deaths out of ~15,500 confirmed cases. The WHO reports signs indicating the virus has peaked in North America and some European countries. However, in the U.S., deaths due to pneumonia and influenza continue to rise past the epidemic threshold.

As few antivirals are available to combat these illnesses, there exists considerable concern, not only for the development of resistance to these drugs, but also for secondary bacterial infections that arise within the current climate of antibiotic resistance.

Pandemic influenza and bacterial infections

Marnie E. Rosenthal1,2 and Barry N. Kreiswirth1
1Jersey Shore University Medical Center, Neptune, NJ and 2Public Health Research Institute, Newark, NJ

On April 12, 2009 the World Health Organization (WHO) requested information regarding an increasing number of acute respiratory illnesses in Veracruz, Mexico. This was determined to be multi-factorial in origin, including seasonal influenza A (H3N2), Influenza B and a novel Swine-Origin Influenza A (H1N1).1

Epidemiologic research into past pandemics of Influenza A, namely the "Spanish flu (H1N1)" pandemic of 1918-1919, the "Asian flu (H2N2)" pandemic of 1957-1958 and the "Hong Kong (H3N2)" flu pandemic of 1968-1969 has provided clues to the increased morbidity and mortality. Viral genome plasticity, such as re-assortment or antigenic shift resulting in new circulating virus subtypes, along with pandemic waves, led to the shift in mortality to younger, otherwise healthy populations. Histological and bacteriologic evidence demonstrate the vast majority of influenza deaths resulted from a viral-bacterial-host interaction with secondary bacterial pneumonia accounting for 50-100 million deaths in the 1918 pandemic.2

In 1945, the first mouse model demonstrating H. influenzae, S. pneumoniae, and S. aureus secondary bacterial pneumonia post-influenza was reported.3 Numerous studies since have attempted to more clearly delineate the molecular mechanism accounting for this interaction. Excellent reviews are available describing

New Research

APUA “cost of resistance” study released

Two-fold higher death rate for patients with resistant infections

In October, APUA and Cook County Hospital announced the release of an eye-opening study on the economic impact of antibiotic-resistant infections. Several studies have examined the medical costs of these infections, but this is the first to conduct a chart by chart review to assess the role of resistance in the course and outcome of the infection. It assessed the cost to families as well.

The study, titled “Hospital and Societal Costs of Antimicrobial Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship” and published in the Oct. 15 issue of Clinical Infectious Diseases (Vol. 49, p.1175-1184), analyzed the medical and human costs associated with antimicrobial resistant infections (ARIs). Initiated by APUA, the study was conducted in collaboration with the Cook County Hospital (currently the John H. Stroger, Jr. Hospital of Cook County) in Chicago, IL and sponsored by an unre...
**New Research**

**Declining antibiotic use for respiratory prescriptions in U.S.**

A new study by Vanderbilt University Medical Center scientists (JAMA, Aug. 19) reports a significant decline in antibiotic prescriptions for respiratory tract infections in the U.S.

Over the past 12 years antibiotic use in children has declined 36%, largely due to educational efforts to reduce inappropriate use, as well as the new pneumococcal conjugate vaccine, which has reduced ear infections in young children. Medical visits for children under 5 years declined 17%, while antibiotic prescription rates fell 27%. Visits for respiratory tract infections in older patients remained relatively unchanged, but antibiotic prescriptions fell 18% for respiratory infections and 24% for other conditions in which antibiotics are rarely indicated.

Dr. Stuart Levy commented, “It’s a wonderful finding. The message is getting out there. There is a major gain in the appropriate use of antibiotics — the realization that if we reduce the inappropriate use of antibiotics, we will control the levels of resistance.”

Despite the overall reported decline, the Vanderbilt study notes that prescriptions for powerful broad-spectrum antibiotics such as azithromycin and the quinolones have increased significantly in the battle against MRSA and other resistant bacteria.
Resistance threat looms for H1N1 antivirals

Genevra Pittman, APUA Staff

Of the very few antiviral drugs available in the U.S., only two, oseltamivir and zanamivir, are currently recommended for treatment of H1N1 influenza. As the flu pandemic continues to emerge worldwide, worry is building that resistance to oseltamivir, the most commonly used antiviral, may increase as well. Oseltamivir, marketed under the brand name Tamiflu®, is known for easing symptoms associated with flu and the duration of illness — when the virus it targets is susceptible to it.

While some developing nations are having trouble obtaining enough of the drug to appease sick or worried citizens, controversy still exists as to when oseltamivir should be prescribed and how to avoid the widespread resistance that has developed with prior strains of influenza. Roche, the company that produces Tamiflu®, advertises its use for both treatment and prevention of the flu, stating that the drug greatly reduces transmission of the flu after possible exposure. Some companies in the U.S., such as the Boston-based law firm Ropes & Gray, have stockpiled the drug en masse to provide to all employees who want it for themselves and their families. The U.S. Department of Health and Human Services has come out against these practices, arguing that most people who get sick don’t need oseltamivir (see guidelines box at right). And the World Health Organization does not recommend that antivirals be used for prophylaxis, in part because more drug consumption means more opportunities for resistance to develop and spread — making the antivirals useless when they are actually needed. These concerns parallel those related to the overuse and misuse of antibiotics.

Oseltamivir works by inhibiting the enzyme needed for virus production, neuraminidase. The drug latches onto cells that play host to the influenza virus and prevents newly created viruses from budding off the host and infecting other cells. But, as with all other antiviral and antibiotic drugs, the target can develop a resistance that makes the drugs ineffective. Resistance starts with a chance mutation, but because drug-resistant viruses have a significant advantage in populations where antivirals are used, they can spread quickly. By mid-December 2008, for example, the Centers for Disease Control and Prevention found that 98 percent of last season’s H1N1 (i.e. “seasonal H1N1”) viruses tested were resistant to oseltamivir.

Ninety-six oseltamivir-resistant strains of the novel H1N1 (2009 “swine variant”) influenza virus have been recorded as of December 2, according to the WHO. In some of these cases, oseltamivir had previously been used in the patient for disease prevention. In all cases, the influenza strain was still susceptible to zanamivir, another major antiviral drug marketed under the name Relenza®. The CDC has reported that 16 of the novel variant H1N1 samples tested between September 1 and November 28 were resistant to oseltamivir (see table below). Two clusters have been identified — in Wales (UK) and in N. Carolina (U.S.).

Adamas Pharmaceuticals has paired with researchers to develop a drug cocktail that incorporates three different current antiviral drugs in an attempt to wipe out viruses before they have a chance to develop resistance to any of the three — oseltamivir, amantadine, and ribavirin. Mark Prichard, an infectious disease and virology professor at the University of Alabama at Birmingham, has said that the combination can effectively treat “seasonal flu” and the current H1N1 virus, including strains that are already resistant to one of the drugs, although testing in human subjects is just beginning.

But for as long as most H1N1 cases remain susceptible to oseltamivir, the focus will be on getting the drug to those who need it, both in the U.S. and in the developing world — where drug access might be more complicated than a doctor’s visit and a prescription, and governments struggle to obtain enough doses of oseltamivir and put it in the right hands.

SOURCES
UAB School of Medicine, medicine.uab.edu.

Who should use antivirals for influenza

- Hospital patients with confirmed or suspected influenza
- Outpatients with influenza-like illness and severe symptoms, such as pneumonia or clinical deterioration
- Persons who are at higher risk for influenza complications:
  - Children less than 2 years old*
  - Adults 65 years and older
  - Pregnant women and women up through 2 weeks post-partum
  - Persons with certain chronic medical conditions (e.g., asthma, heart failure, chronic lung disease) and those with weak immune systems (e.g., diabetes, HIV)
  - Persons younger than 19 years of age who are receiving long-term aspirin therapy

*Children aged 2-4 also have a higher rate of complications, but their risk is lower than those below age 2.
source: www.cdc.gov

Antiviral resistance among US isolates of 2009 H1N1 (“swine variant”)*

<table>
<thead>
<tr>
<th></th>
<th>Oseltamivir (Tamiflu®)</th>
<th>Zanamivir (Relenza®)</th>
<th>Adaminantes: Ramantadine (Flumadine®)</th>
<th>Amantadine (Symmetrel®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samples tested</td>
<td>1540</td>
<td>451</td>
<td>207</td>
<td>206</td>
</tr>
<tr>
<td>Samples resistant</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
<td>99.5</td>
</tr>
</tbody>
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*as tested by the CDC; source: www.cdc.gov (12/06/09)
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<tr>
<th></th>
<th>“Seasonal” flu</th>
<th>H1N1 (&quot;Swine&quot;) flu</th>
</tr>
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<tbody>
<tr>
<td><strong>When is flu season?</strong></td>
<td>Flu season begins in the fall and usually peaks in mid-winter.</td>
<td>The first cases of H1N1 were reported in April, and it caused deaths through the summer – very uncommon for seasonal flu.</td>
</tr>
<tr>
<td><strong>What are the symptoms?</strong></td>
<td>The most common flu symptoms include fever (greater than 100 degrees F), cough, sore throat and fatigue.</td>
<td>Symptoms are similar to seasonal flu, but more cases of vomiting and diarrhea have been reported.</td>
</tr>
<tr>
<td><strong>How is it treated?</strong></td>
<td>Antiviral drugs are prescribed to those with serious cases of seasonal flu.</td>
<td>Antivirals are also prescribed for serious cases of H1N1.</td>
</tr>
<tr>
<td><strong>Who is most at risk for contracting the flu?</strong></td>
<td>Adults 65 and older and young children, along with pregnant women and those with preexisting medical conditions, are most at risk for contracting the flu.</td>
<td>The highest proportion of reported cases have come in those aged 5-24. Pregnant women and those with preexisting medical conditions are also at an elevated risk.</td>
</tr>
<tr>
<td><strong>Who should get vaccinated?</strong></td>
<td>Everyone, but especially pregnant women, children 6 months to 19 years, adults over 50, and the chronically ill and those who care for them.</td>
<td>Pregnant women, children and young adults 6 months to 24 years, adults aged 25 to 64 who have chronic health conditions, adults with compromised immune systems, healthcare personnel and people who care for infants less than 6 months old.</td>
</tr>
<tr>
<td><strong>Who is most at risk for mortality?</strong></td>
<td>Along with those with preexisting conditions, older adults have by far the highest mortality: 90% of U.S. flu deaths occur in those aged 65 and older.</td>
<td>Along with those with preexisting conditions, young and middle aged adults have the highest mortality: 65% of U.S. H1N1 deaths have been in those aged 25-64.</td>
</tr>
<tr>
<td><strong>How many people die from complications?</strong></td>
<td>About 36,000 people in the U.S. and 250,000 to 500,000 globally die from flu complications annually.</td>
<td>So far, just over 1,800 people in the U.S. and more than 8,700 globally have died from complications of H1N1.</td>
</tr>
</tbody>
</table>


**PANDEMIC continued from page 1**

Theorized mechanisms, including neuraminidase-induced bacterial adherence and upregulation of influenza infection; interleukin 10-induced susceptibility to pneumococci and possibly staphylococci; and virus-induced desensitization to bacterial Toll-like receptor ligands.9

Morens et. al. examined lung tissue banked in the National Tissue Repository of the Armed Forces Institute of Pathology from 58 autopsies during the 1918 influenza epidemic and confirmed that a desquamative tracheobronchitis or bronchiolitis was most commonly due to S. pneumoniae.11 During the 1957-1958 Asian flu pandemic, secondary bacterial pneumonia was also linked to increased mortality, however, negative lung cultures were more common, and a shift toward Staphylococcus aureus predominance was noted. The increase in S. aureus and the more frequent negative lung cultures are potentially attributable to the selective pressure from utilization of the semi-synthetic penicillins introduced in the 1950s.

In the 1968-1969 Hong Kong influenza pandemic, a single center experience in Atlanta, GA documented a three-fold increase in the incidence of staphylococcal pneumonias when compared with the prior 1957-1958 time period. During the epidemic influenza period, patients with staphylococcal pneumonia were, on average, 22 years younger. Only 43% had a comorbid medical condition, as compared with 100% during the non-epidemic year prior.12

During the 2003-2004 seasonal influenza period, the CDC evaluated 153 cases of influenza-associated deaths in children reported by 40 state health departments. Of those influenza cases, 123 were Influenza A (predominantly H3N2) and three cases were Influenza B. Laboratory-confirmed bacterial coinfecions were identified in 24 of 102 cases (24%) for which culture results were reported. Staphylococcus aureus infection was seen in 11 cases, of which six involved a methicillin-resistant strain.1

The rapidity of MRSA clonal spread, as evidenced by the recent dramatic increase in MRSA, specifically USA300, was initially described in patients without health-care associations, and thus termed community associated (CA)-MRSA. In 2002, Gillet et. al. published a series of fatal necrotizing S. aureus pneumonia associated with a post-influenza syndrome. Of these eight cases of community acquired S. aureus pneumonias, six were fatal and all had a preceding influenza-like illness.7 Severe post-influenza-associated, community-acquired necrotizing pneumonias have been described — most recently associat-
Antibiotic resistance is here to stay. This disheartening reminder comes from the American Academy of Microbiology in its recent report, “Antibiotic Resistance: An Ecological Perspective on an Old Problem.” The report is the result of a colloquium convened October 12-14, 2008 on antibiotic resistance and the factors that influence its spread. But while antibiotic-resistant bacteria will never be completely eliminated, the report outlines ways that resistance can be more effectively contained in both the developing and developed worlds. It also calls for increased communication between scientists examining trends of resistance and the public.

Antibiotic resistance, the report says, is a result of both the appropriate and inappropriate uses of antibiotics. Even when antibiotics are used appropriately, increased selective pressure means more opportunities for bacteria to acquire resistance. This potential is magnified when antibiotics are used unnecessarily, such as to “treat” the flu or a cold. This is especially problematic in developing countries, where antibiotics may be widely available without a prescription and education on the proper use of these drugs is lacking.

Once antibiotic-resistant bacteria strains develop, they can spread rapidly across a population — whether that population is a village or a hospital — through poor hygiene and unsanitary conditions. These drug-resistant pathogens can be passed directly between individuals, leak into the environment through contaminated waste, and exchange genetic resistance elements with other bacteria.

Given the emergence and high cost of antibiotic resistance, the Academy outlines a number of suggestions for preventing the spread of resistant bacteria. Paramount to this effort is improving hygiene through education, training and implementation of regulations in clinical settings. The report calls for more rapid diagnosis of patients who may have a resistant infection, increased antimicrobial susceptibility testing, and improved surveillance to track the evolution and spread of various strains of resistant bacteria. Government regulation of antibiotic prescription and use in all countries should be strengthened to prevent unnecessary use and limit the development of new resistant bacteria.

Finally, the report states the importance of increased dialogue between the bench scientists working in the field of antibiotic resistance and members of the public and policy makers who will ultimately be responsible for putting into action efforts that will harness its spread.

American Academy of Microbiology releases report on antibiotic resistance
COST OF RESISTANCE continued from page 1

stricted educational grant from bioMérieux and the Centers for Disease Control and Prevention.

The authors employed a uniquely exhaustive review of 1,391 patients hospitalized in the year 2000, 188 of whom had ARIs (13.5%). The medical costs attributed to these ARIs ranged from $18,588 to $29,069 per patient, while the duration of hospital stay was extended 6.4 - 12.7 days for affected patients. Additionally, the excess mortality attributed to ARIs alone was 6.5% — a death rate two-fold higher than in patients without ARIs. The authors also estimated the societal costs incurred at this hospital as a result of the ARIs to be between $10.7 and $15 million, which is the cost that hits the families of those infected.

Antibiotic resistance is fueled by misuse and overuse of antibiotics. Bacteria become resistant to the very medicines developed to treat and cure the infection they cause. ARIs include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE) and a growing number of additional pathogens that are developing resistance to many common antibiotics.

“The findings indicate that significant health and economic benefits could be realized through effective interventions to reduce antimicrobial-resistant and healthcare-associated infections,” according to Dr. Rebecca Roberts, Department of Emergency Medicine, Cook County (Stroger) Hospital and the lead study author.

“At a time when our country is debating how to deliver better, more affordable care, this study demonstrates the enormous cost savings that could be realized, for both the healthcare system and to individuals and their families. These costs will only continue to increase if we don’t amend our behavior and practice a more prudent usage of antibiotics,” said Dr. Stuart Levy, Professor of Medicine at Tufts University School of Medicine, a senior author of the paper and co-founder and president of APUA, which initiated the study in accord with its mission to preserve the power of antibiotics.

Extrapolating the costs nationwide

“The results offer some good insight regarding just how much ARIs are costing the nation: not just in terms of dollars, but human life and suffering,” said Dr. Levy. “As the enormous costs identified here are viewed on a national scale, it is clear that effectively addressing the issue of antimicrobial-resistant infection is an essential element for stemming the rising tide of healthcare costs in the United States.”

“Further study is required, specifically to see how much we could save on a national level if we took some basic steps to halt the development of resistant infections and their spread within hospit-

“Clearly, any discussion of healthcare reform must look at the cost of current clinical practice and the savings we could realize if we used antibiotics more prudently.”

— Rebecca Roberts, M.D.

and $5.2 billion a year and between $5.7 and $11.3 million in additional days in the hospital. Clearly, any discussion of healthcare reform must look at the cost of current clinical practice and the savings we could realize if we used antibiotics more prudently,” noted Dr. Roberts. “Imagine if these hospital beds and healthcare resources were used instead for preventive care or for underserved patients,” she added.

“Assuming 900,000 ARI cases in the year 2000, based on the conservative selection criteria used in our study, the total societal costs of ARIs to U.S. households in the year 2000 was approximately $35 billion,” Dr. Roberts added. “This includes lost wages from extended hospital stays and from premature deaths.”

“Keep in mind these data were collected in 2000, and the rate of notifications of antibiotic resistant cases has more than doubled since then, so these figures should be viewed as very conservative. Further work is ongoing to estimate the current burden at state and national levels,” said Prof. Susan Foster, a co-author and health economist at APUA.

“Another mitigating factor that may also cause us to underestimate the true burden is the excellent clinical practice where the study actually occurred,” said Dr. Levy. “To its credit, Cook County (Stroger) Hospital happens to have an enviably low rate of healthcare associated infections, including ARIs.”

A study suggested by the late Senator Edward M. Kennedy

In discussions with the late Senator Edward M. Kennedy on the topic of drug resistance and healthcare, “I spoke frequently with Senator Kennedy about the avoidable costs from the misuse of antibiotics,” Levy said. “Without fail, the senator always concluded our discussions on the topic by telling me that we need to quantify the cost of treating
COST OF RESISTANCE continued from page 6

antibiotic-resistant infections in order to make any real progress toward an appropriate policy for antibiotic stewardship. In a very real sense, this study grew from those talks with the late senator.”

“This study is the first to quantify the alarming impact of antibiotic-resistant infections on treatment costs and patient outcomes,” said Herb Steward, general manager and executive vice president of bioMérieux North America, which funded this study. “It also highlights the vital role of simple, rapid and cost-effective diagnostics in order to get the right information to clinicians as fast as possible so they can treat patients appropriately and use antibiotics prudently, while improving care and patient outcomes and reining in unnecessary costs.”

Societal impact more than just financial

“The societal financial impact of $15 million based on just over 188 cases of ARI is an alarming finding,” said Dr. Robert A. Weinstein, interim chairman, Department of Medicine, Cook County (Stroger) Hospital, Professor of Medicine at Rush University Medical College, and a senior author and initiator of the project at Cook County (Stroger) Hospital. “Sustaining these kinds of costs is simply not tenable for individual families and for the economy at large. With healthcare reform and the focus on the direct cost of care, this study should remind us that every dollar spent to treat avoidable illness ripples throughout society and has an impact on individual, family, community, and corporate budgets across the nation.”

The additional cost of patient care resulting from ARIs is not the only aspect of this study that has relevance to the ongoing debate over healthcare reform. “One topic that all parties seem to find agreement on is the need to bring healthcare information technology into the 21st century,” said Dr. Weinstein. “We at Cook County (Stroger) Hospital have adopted an electronic medical records (EMR) system, which made the review of literally thousands of pages of patient records and lab results infinitely easier. However, most hospitals in the U.S. still do not have EMR systems, so this kind of review would be nearly impossible.”

“Thanks to the leadership of the Centers for Disease Control and Prevention’s National Healthcare Safety Network (NHSN), hospitals like ours have the tools and protocol to track ARIs,” Dr. Weinstein added. “However, this is a voluntary program. Several states mandate that their hospitals comply with NHSN protocols, but most do not. Until we have a uniform standard for reporting and disclosure, we may never know the true cost of these avoidable infections.”

REFERENCE

Figure 1. Costs of antimicrobial-resistant infections (ARI) in a U.S. teaching hospital

Adapted from Clin Inf Dis 2009;49:1175-84

The average per-case cost of treating antibiotic susceptible (N= 1203) versus antibiotic-resistant (N= 188) infections, and resistant cases sorted by hospital-acquired and community-acquired infections: MRSA = methicillin-resistant Staphylococcus aureus (N = 81), VRE = vancomycin-resistant enterococci (N = 58), AREK = Escherichia coli resistant to fluoroquinolones or third-generation cephalosporins or Klebsiella species resistant to third-generation cephalosporins (N = 30) and AIR = amikacin- or imipenem-resistant Enterobacter, Pseudomonas, or Acinetobacter species (N = 8).
**New Research**

**New GRACE study in EU advocates standardized antibiotic prescribing**

In the largest prospective study of its kind, researchers of the EU-funded Genomics to Combat Resistance against Antibiotics in Community-acquired LRTI in Europe (GRACE collaborative) conducted a survey of 3,402 adults with acute cough, recruited from 13 European countries (Wales, England, The Netherlands, Spain, Germany, Hungary, Belgium, Poland, Italy, Sweden, Norway, Finland and Slovakia). Medical histories, existing conditions, symptom severity and management were evaluated and followed for 28 days. The results, published in the British Medical Journal (C.C. Butler et. al., BMJ, 338:2242, doi 10.1136/bmj.b2242), have revealed wide variation in antibiotic prescribing for acute cough. Overall, antibiotics were prescribed for 53% of patients (range = 21% to nearly 90%) across the networks and there were radically divergent antibiotic choices. The most common prescription, amoxicillin, ranged from 3% in Norway to 83% in England. In Milan, over 15% of patients received a fluoroquinolone. Despite the marked variation, patients recovered at a similar rate, regardless of whether an antibiotic was prescribed. The study authors concluded that antibiotics are still considerably over-prescribed for acute cough and that the large differences in prescriptions are not clinically justified. GRACE coordinator Professor Hermann Goossens stated, “This threat of antibiotic resistance is likely to be dramatically heightened as GPs face increasing demands to prescribe antibiotic for acute cough, amidst the current global H1N1 flu pandemic. The evidence presented by the GRACE study…could prove instrumental in containing antibiotic prescribing.” The authors advocate standardizing antibiotic prescribing for respiratory illnesses. GRACE is poised to provide a platform for developing interventions that are generic, but sensitive to the local context.

More information on the GRACE collaborative may be found at https://www.grace-lrti.org.

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**APUA remembers Senator Edward Kennedy**

Senator Edward Kennedy understood the need to preserve the power of antibiotics through more prudent antibiotic use. In 2002 he called the first bipartisan Congressional hearing focused on drug resistance with Republican Senator Bill Frist from Tennessee. Recognizing that drug resistance issues demand priority status on the nation’s agenda, he urged APUA to document the cost implications in order to gain the attention of policy makers. APUA accepted this challenge and initiated a research project with a major U.S. teaching hospital. The product of this effort is a recent Clinical Infectious Diseases article (Oct 15, 2009;49:1175-1184) which demonstrates the real healthcare costs of antibiotic resistance infections in U.S. hospitals (see summary, p.1) and how the related dollar and human costs rival those of the H1N1 flu which is receiving more attention. We at APUA sorely miss this strong champion of public health, but shall continue to remember his recommended legislative strategies.

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**APUA staff and colleagues produce unique volume reviewing AMR in developing countries**

APUA’s International Program Director, Aníbal de J. Sosa, MD and several APUA colleagues are co-editors of a new book, Antimicrobial Resistance in Developing Countries, published by Springer. The book gives a picture of existing and emerging threats of antimicrobial resistance for bacterial infection, HIV, malaria, tuberculosis, fungal and selected parasitic infection in regions of the world where lack of funding and attention result in dangerous consequences. This work broadens the conversation, pooling resources of existing data, trends and risk factors from researchers working in resource-poor countries where it has largely been ignored. APUA staff and chapter leaders also contributed to this 556-page volume.

APUA advocates for more data from food animal production

APUA responded to a recent Federal Register notice soliciting comments on how to improve reporting of data on antibiotics used in food animal production in the U.S. APUA’s suggestions were to expand proposed regulations on manufacturer reporting to include all food animal products containing antimicrobials and to introduce surveillance regulations that would obtain specific end-user data on antimicrobial use from veterinarians and animal owners. APUA believes that increased surveillance will allow for improved risk assessment and models to determine the link between antimicrobial use in agriculture and resistance in humans, and will better guide public health policy to help preserve antimicrobial effectiveness. See the APUA letter in its entirety at www.apua.org. (Public Policy Actions)

New trans-Atlantic task force on antimicrobial resistance

A November 3 White House communiqué covering the U.S.-EU Summit highlights antimicrobial resistance as one of the three greatest global health threats. On the last evening of the Summit, the White House announced that a working group on antimicrobial resistance would be appointed to develop a concrete action plan. The mission of the task force will be to discuss the most pressing issues related to antibiotic resistance and then develop an action plan that will address these areas. It will focus on ensuring the prudent use of antimicrobials in both human and veterinary medicine, along with preventing the spread of drug-resistant infections and establishing incentives for the production of new antibiotics. A report is expected at the 2011 Summit.

This international agreement demonstrates the recognition that antibiotic resistance is not a national problem — that antibiotic use and misuse in any country influences effectiveness every-where, and thus strategies for resistance containment must be approached on a global level.

Strengthening scientific evidence to control misuse of antibiotics in agriculture

A recent op-ed by Dr. Stuart Levy was carried in major U.S. news outlets, including the LA Times and the Chicago Tribune, noting that Congress and President Obama’s administration are missing a key remedy for preserving the health of Americans and limiting costs. In “An unusual prescription for health care,” (Nov. 5 op-ed, MCT News Service), Dr. Levy strongly advises the government to reduce the development of antibiotic-resistant bacteria through stopping the use of antibiotics as growth promoters in food animal production. Although the Federal government has cautioned doctors to prescribe antibiotics only for patients with bacterial infections, regulations do not address the large-scale use of antibiotics in livestock feeding operations found on industrial farms. The Union of Concerned Scientists maintains that approximately 70% of antibiotics sold in the U.S. are for non-therapeutic use in food animals, i.e. for animals that are not sick. The European Union has banned non-therapeutic use of antibiotics in food animal production and APUA and Dr. Levy advocate that the U.S. should follow suit.

The fundamental scientific principles that support a ban on growth promotion are not well understood or easily conveyed. Based on APUA’s long standing advocacy for evidence based policy and related scientific articles in medical journals (The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences, Clin Infect Dis Vol.34, Supplement 3). APUA has received funding from The Pew Charitable Trusts to conduct research and policy activities to increase understanding of the need to improve antibiotic use in food animal production.

Updates on U.S. legislative activities

On the legislative front, addressing the problem of antimicrobial resistance are the pending passage of the Preservation of Antibiotics for Medical Treatment Act (PAMTA), the Strategies to Address Antimicrobial Resistance Act (STAAR Act), and the increase in industry reporting requirements through the Animal Drug User Fee Amendments (ADUFA) of 2008 — Federal, Food, Drug and Cosmetic Act.

PAMTA — PAMTA would require the FDA to review approvals previously issued for animal feed uses of seven classes of antibiotics important to human health and withdraw approvals for those drugs that pose a threat. Senator Diane Feinstein is going to be a champion for PAMTA — taking up the work of Senator Kennedy, who introduced the bill along with Louise Slaughter. Ten Congress men and women are confirmed for supporting the bill, four of whom are Republicans.

STAAR Act — if passed, will serve to: strengthen research to reduce inappropriate use of antibiotics; develop/test new interventions to limit the spread of resistance; and create new tools to detect, prevent and treat drug-resistant infections. There has been little recent activity concerning this as Congress has been focusing on health care reform. It is expected that soon hearings will resume in the House of Representatives. For updates on legislative activities, see the policy/advocacy section on the website for the Infectious Disease Society of America, www.idsociety.org.

ADUFA — to insure that the FDA has the relevant information to examine safety concerns about the use of antibiotics in food-producing animals, these amendments require that the sponsor of each new animal drug that contains an antimicrobial agent submits an annual report to the FDA. This report would contain the amount of each antimicrobial active ingredient in the drug that is sold or distributed for use in food-producing animals, including information on any distributor-labeled product.
International biosecurity project draws on APUA bench, field work, and public health skills

In collaboration with the NBACC’s National Biological Threat Characterization Center (NBTC), APUA’s International Surveillance of Reservoirs of existing void for global public health assessments by providing the specimens and data needed to better understand the diversity of resistance genes and the potential emergence of novel genotypes. The project supports international biosecurity efforts to assess the threat potential of the genotypes and phenotypes of resistant bacteria found in the global biome which have the possibility of being utilized as enhancers of agents of biological terrorism.

During the initial phase, ~700 soil, water and animal isolates of *Escherichia coli*, *Staphylococcus*, *Streptococcus*/*Enterococcus* and *Salmonella* were collected and characterized from Georgia, India, South Korea, Turkey and Uganda. The ISRAR project employs APUA’s basic bench capacity as well as the organization’s global network and public health staff and databases at APUA headquarters. In efforts to expand collection to more countries, ISRAR project Manager Dr. Anibal Sosa recently visited laboratory sites in Vietnam and South Africa. These countries, in addition to Bangladesh, will engage in collection of isolates from watersheds and large tributaries, with a focus on species of *Pseudomonas*, *Aeromonas*, *Acinetobacter* and *Stenotrophomonas*. In collaboration with Tufts University School of Medicine, all isolates will be speciated and tested for antimicrobial susceptibility. Strains will then be transported to collaborators in the Center for Microbial Ecology at Michigan State University for microarray and rapid whole genome sequencing.

**APUA News**

**Antibiotic Resistance** (ISRAR) project continues to collect and analyze environmental and veterinary commensal organisms that may serve as reservoirs for antibiotic resistance genes. This project investigates the potential for a surveillance system capable of tracking and analyzing patterns of antibiotic resistance in commensal bacteria over a multi-year period on a global scale. The surveillance system will fill an APUA-sponsored article, “Sustainability for behaviour change in the fight against antibiotic resistance: a social marketing framework” by Stephanie Boyd and Tim Edgar (Journal of Antimicrobial Chemotherapy. 2009;63:230-7. Epub 2008 Dec 18), as well as APUA’s latest publication on the cost of resistance (see page 1). Dr. Foster, Dr. Lauri Hicks, DO, the Medical Director of *Get Smart* and Rebecca Roberts, MS, Public Health Specialist of *Get Smart* held discussions on the potential of future APUA/CDC research collaborations.

**APUA 2009 Leadership Award presented to IDSA**

APUA Scientific Advisory Board Members, Chapter Leaders and Corporate Colleagues gathered for the APUA annual Member Reception and Leadership Award Presentation at the Annual Interscience Conference on Antimicrobial Agents and Chemotherapy in San Francisco on September 14, 2009. This year APUA gave special recognition to the Infectious Diseases Society of America (IDSA) for its “exemplary leadership in promoting government action to improve antibiotic use and contain antibiotic resistance.”

“IDSA has been a vital partner in our work to preserve the power of lifesaving antibiotic drugs while encouraging the discovery of new antibiotics to tackle dead-

**U.S. CDC meets with “MinuteClinics” and APUA**

On October 1, Dr. Susan Foster represented APUA at a U.S. CDC invitation-only meeting. The purpose of this “Retail Pharmacy Summit” was to bring together industry, CDC, academic medical staff, NGO’s and others concerned about appropriate antibiotic use, especially through the retail pharmacies and “MinuteClinics” which have proliferated recently. Dr. Foster distributed an “APUA Research Brief” based on the

**Anthony I. Okoh, PhD, ISRAR Country Laboratory Leader and Professor of Microbiology & HOD, University of Fort Hare, Alice, South Africa explaining the water treatment process for the removal of microbial and chemical contaminants.**

**Dr. Anibal Sosa, APUA ISRAR project manager, (right) with Vo Thi Tra An, DVM, PhD, (second from right) and her colleagues from the Dept. of Veterinary Pharmacology & Internal Medicine, Nong Lam University, Ho Chi Minh City, Vietnam.**

**APUA bestows its annual Leadership Award to representatives of the IDSA. From left to right: Thomas O’Brien, MD, APUA vice president; Martin Blaser, MD, FIDSA, IDSA past president; Neil Fishman, MD, chair of IDSA’s Antimicrobial Resistance Work Group; Stuart B. Levy, MD, APUA president; Kathleen Young, APUA executive director.**
ly infections,” said APUA president Stuart B. Levy, MD in presenting the award.

Over the past several years, IDSA has formed an active coalition with APUA and other national organizations to urge Congress to improve the nation’s approach to antibiotic resistance by passing the Strategies to Address Antimicrobial Resistance (STAAR) Act. Martin Blaser, MD, FIDSA, a past president of IDSA, and Neil Fishman, MD, chair of IDSA’s Antimicrobial Resistance Work Group, accepted the award for IDSA. In his acceptance speech, Blaser noted that up to 50% of antimicrobial use is inappropriate, adding considerably to the nation’s health care costs.

The STAAR Act (H.E. 2400), which IDSA took a leading role in crafting, would help contain the spread of antimicrobial resistant “bad bugs” through better coordination and funding of federal activities, stronger surveillance, prevention and control efforts and research.

APUA is currently accepting nominations for its 2010 Leadership Award. Nomination forms, as well as a list of past APUA awardees, can be found at www.APUA.org.

APUA field research activities expand into Zambia

APUA’s Antibiotic Situation Analysis and Needs Assessment project, funded by the Bill & Melinda Gates Foundation, is designed to evaluate antibiotic use and resistance in the African countries of Uganda and Zambia. The goal is to guide evidence-based interventions to reduce mortality due to pneumonia and diarrheal diseases. Fieldwork in Uganda, in which laboratory, hospital, pharmacy and drugseller data are collected, has been completed on schedule by a team of 90 Makerere University students. Data cleaning and analysis are underway and active data collection has now moved into Zambia.

A group of 17 pharmacists and pharmacy students received a three-day training course led by project directors Drs. Susan Foster and Anibal Sosa at APUA’s field office in Lusaka, prior to departure for the fieldwork at eight sites around Zambia. The field workers will carry out interviews with health staff at hospitals and health centers on prescribing practices and the staff’s knowledge of antibiotic resistance; document the stock levels of antibiotics; interview pharmacy attendants and informal sector drug sellers; and collect drugs for drug quality testing. Students reviewed the various questionnaires and other instruments for data collection, practiced use of the GPS units to record the locations of drug sellers and pharmacies, and received training in data entry and basic statistical analysis. Working in teams of four, they will spend about five days at each site. Once field data collections are complete, the students will participate in data cleaning and analysis.

APUA-Kenya Chapter News

APUA-Kenya Chapter leader Dr. Sam Kariuki participated in the GARP-Kenya inaugural meeting held August 6-7 in Nairobi. GARP (Global Antibiotic Resistance Partnership), a project of Resources for the Future (RFF), with funding from the Bill & Melinda Gates Foundation, is a worldwide effort to address the challenge of antibiotic resistance. The meeting involved representatives of international and non-governmental organizations, government officials, and experts working in the antibiotic resistance field. Dr. Kariuki, Director of the Enteric Microbiology Laboratory at Kenya Medical Research Institute and GARP-Kenya National Working Group chair, highlighted public health and policy issues that impact the problem of antibiotic resistance in East Africa. Conference participants presented evidence that infectious bacteria exhibit high levels of resistance to common antibiotics; that inadequate surveillance facilities hinder hospital infection control measures; and that vaccination is a potential, underutilized intervention. It is anticipated that a situation analysis, coupled with a program of policy research, will enable the development of national policy strategies for better resistance containment.

APUA-Bulgaria Chapter News

On November 18, APUA-Bulgaria participated in “European Antibiotic Awareness Day” by presenting two educational posters promoting the importance of prudent antibiotic use as a means of turning the tide on antibiotic resistance. The event was sponsored by the ECDC (European Center for Disease Prevention and Control) and ESMID (European Society of Clinical Microbiology and Infectious Disease). For more information see http://ecdc.europa.eu/en/EAAD/Pages/Home.aspx.
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.