Ten years ago, the 20th Anniversary celebration for APUA took place in Chicago. How timely that we return to this city for our 30th Anniversary. In the context of the remarks I made in 2001, let us look back three decades, from the origins of APUA to the current and accomplished activities of our organization.

Founded in 1981, APUA emerged from a meeting in the Dominican Republic, when individuals from developing and industrialized countries came together to discuss a common problem most evident in developing countries – resistance to antibiotics. The issue was made more critical in resource-poor countries where new antibiotics emerging in the industrialized nations were too costly and not readily available to treat individuals with multidrug-resistant infections in developing nations. Consequently, lives were lost that might have been saved.

Discussions at the meeting in Santo Domingo urged greater awareness of the problem. There was a push to establish an organization that was global, which dealt with the issue of antibiotic resistance. The words were carefully chosen. It arose on the heels of a time-coordinated press release simultaneously in four countries (Mexico, Brazil, Dominican Republic, and the United States).

By an “alliance,” it was meant that there would be different groups as well as individuals, which would address local problems and mount efforts in their own countries. These groups would then, join together to form an international organization which dealt with this problem locally and internationally, helping each other.

We have grown enormously since 1981, and certainly over the past decade, with successful funding from foundations and government and non-government public health institutions such as The Bill and Melinda Gates Foundation, the Department of Homeland Security, the Agency for International Development, the Centers for Disease Control and Prevention, and the National Institutes of Health. A number of reports have been issued, including the 2001 book accompanying the WHO report on containment of antimicrobial resistance, summarizing the recommendations of 25 different expert groups for dealing with resistance.

Studies have examined public attitudes toward antibiotics and resistance. Others have looked at commensal bacteria as reservoirs of drug resistance genes. We have also (Continued on page 2)
(Continued from page 1)
examined the impact of antibacterial-surface household products on the control of microbes versus their effect on selecting microbes that are resistant not only to the biocide, but also to antibiotics.

Unfortunately, we have still not made definitive progress in our quest to remove antibiotics from animal feeds. This is not the case in Europe, where the EU has banned this practice and has continued to raise animals for food production without the need for supplementation of the feed. We can hope that, with activities such as PAMTA, the STAAR Act, and other initiatives coming through Congress, as well as the activities of the FDA and the Food Safety Bill, we shall see the removal of antibiotics from animal feeds in the United States and other countries that have not yet followed Europe’s initiative.

As in other areas, the advancement in Internet activities and social networking has helped in our efforts to increase awareness of antibiotic resistance and proper use of antibiotics.

APUA now has its own blog and Twitter account. We have membership in over 100 countries, and have now, in the last 10 years, gone from about 22 country chapters to 66, with a large number of them in the developing world, including Africa. The APUA Newsletter has been continually published since the beginnings of APUA. It remains our first and longest-sustained product and is now electronically distributed free to outside members and non-members all over the world. In some places, it is the only piece of current information on antibiotics and resistance available to individuals in remote parts of the world.

With increasing awareness of this issue, and the continued concern expressed by the World Health Organization (including dedication of World Health Day to the issue of antibiotic resistance this year), we can look forward to advancement in these activities over the next years. I optimistically hope to report on our 40th Anniversary that we have, in fact, overcome many of the obstacles we currently face, and that many others have been improved upon.

Speaking for myself, the Board, and other staff members here at APUA, I thank you for your continued support, and welcome your comments and news of local activities where we can help.

(Continued from page 1)
Goals of the symposium include recognizing major drivers of antibiotic resistance, comparing promising interventions (such as diagnostics, vaccines, and stewardship programs), evaluating and prioritizing major antibiotic development needs, and developing effective strategies to control the emergence and spread of antibiotic resistance this year), we can look forward to advancement in these activities over the next years.

APUA Project Partners:

- The Bill and Melinda Gates Foundation
- The PEW Charitable Trusts
- U.S. National Institute of Health (NIH)
- Pan American Health Organization (PAHO)
- U.S. Agency for International Development (USAID)
- U.S. Department of Agriculture
- U.S. Office of Homeland Security
- National Biodefense Analysis and Countermeasures Center (NBACC)
- World Health Organization (WHO)
- Centers for Disease Control and Prevention (CDC)
- U.S. Food and Drug Administration (USFDA)
- World Bank
- Ministries of Health

APUA Corporate Sponsors:

- Leadership Level - $25,000
  - bioMérieux Inc.
  - The Clorox Company
- Benefactor Level - $15,000
  - AstraZeneca
- Partner Level - $10,000
  - Bayer Healthcare Pharmaceuticals
  - Alcon Laboratories
  - GlaxoSmithKline
- Supporting Level
  - Paratek Pharmaceuticals
antibiotic resistance.
The session will be moderated by Dr. Stuart Levy (Professor of Molecular Biology and Microbiology and Medicine, Tufts University), Dr. Keith Klugman (Professor of Global Health and Medicine, Emory University) will speak on "The Impact of Vaccines on Resistance in the U.S. and Developing Countries." Dr. Iruka Okeke (Associate Professor of Molecular Microbiology, Haverford College) will present "Drivers of Resistance and the Role of Diagnostics in Resource-Limited Settings," and Dr. Sherwood Gorbach (Emeritus Director of the Nutrition/Infection Unit, Tufts University) will address "The Role of Narrow-Spectrum Agents and Novel Mechanisms of Action in Containing Resistance."

**Annual International Member Reception: September 18, 7 PM**
(RSVP to jennie.choe@tufts.edu)

Please join friends and colleagues at the APUA 30th Anniversary Celebration in the Prairie Center Lobby of the Hyatt Regency McCormick Place, to be held from 7 PM to 9 PM on Sunday, September 18. At the reception APUA will present its 2011 Leadership Award to Dr. Giuseppe Cornaglia, chairman and president of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). The award recognizes Dr. Cornaglia and ESCMID for their invaluable work in establishing effective expert study groups and educational initiatives in developing countries to control antibiotic resistance and improve treatment.

The 2011 Chapter Leadership Award will be awarded to the APUA Nepal chapter and its president, Dr. Kumud K. Kafle (Professor and Head of Clinical Pharmacology at Tribhuvan University Teaching Hospital). The award recognizes the extraordinary multi-hospital coordination the chapter has done to increase practitioner awareness of antibiotic resistance trends and guidelines in the Kathmandu region.

APUA-Nepal is part of APUA’s worldwide network of affiliated organizations located in more than 66 countries, 33 in resource poor countries. For over eight years, Dr. Kafle and his team of APUA-Nepal leaders have tested the sensitivity patterns of common pathogens, consolidating data from a network of hospitals under the Nepal Department of Health Services that includes eight central hospitals, three regional hospitals, two sub-regional hospitals, 10 zonal hospitals, and 65 district hospitals.

The antibiotic susceptibility information that they gathered has been invaluable in guiding antibiotic treatment in the region, and has led to the publication of the Nepal National Antibiotic Treatment Guidelines that addresses all aspects of common infectious disease treatment from primary to tertiary care. APUA-Nepal has also published an article on "Antimicrobial resistance at different levels of health care services in Nepal" in the Regional Health Forum (published by SEARO/WHO) this year, and presented at a WHO Regional Meeting on the Rational Use of Medicines in 2007.

Last year’s Chapter Leadership Award was presented to the APUA Mexico chapter and its president, Dr. Miguel Peredo López-Velarde, for introducing strong national surveillance, education, and legislation to improve antibiotic use in Mexico.

**The Need for Improved Diagnostics: Harder Better Faster Stronger**

**Jennie Choe, M.S.**
Assistant Editor
**Alliance for the Prudent Use of Antibiotics**

Antibiotic resistance is considered by health authorities such as WHO and CDC to be one of the greatest public health threats facing the world today. Staggering rates of mortality, morbidity, and economic cost give weight to this claim. 440,000 cases of multi drug-resistant tuberculosis emerge annually and result in more than 150,000 deaths. Extensively drug-resistant tuberculosis has been reported in 69 countries to date, and most malaria-endemic countries are showing resistance to earlier generation antimalarial drugs. As recently as 2007, MRSA was responsible for more annual deaths than AIDS. An APUA-sponsored study published in Clinical Infectious Diseases also found that in 2000,
as antibiotic-resistant infections were responsible for anywhere from $18,588 to $29,096 in medical costs per patient, and 6.4 to 12.7 extra days in the hospital. In a single hospital that year the costs of treatment, extended hospital stays, and lost wages added up to $15 million – an estimated $35 billion nationwide.

As antibiotic resistance wreaks havoc among individuals, communities, and health facilities, the need has never been greater for effective clinical diagnostic tests. The most valuable diagnostic tests are those that can 1) rapidly identify a pathogen, 2) determine its antibiotic resistance profile, and 3) be used to choose and immediately initiate the best therapy. Ideally, they should also be sensitive and specific, fast, cheap, user-friendly, and ready for use on native samples at a patient’s bedside.

These are high standards worth striving for. Early diagnosis and immediate initiation of an appropriate antibiotic treatment can greatly improve the outcomes of many different types of infections. Conversely, during some systemic responses to infection (such as sepsis), every hour of delay in the administration of the right treatment is associated with a 7% rise in mortality. In the case of pathogens that are similar in morphology to harmless bacteria (such as coagulase-positive S. aureus), a mistaken or delayed diagnosis can cause patients to be treated unnecessarily with broad-spectrum antibiotics or to be given inadequate doses of antibiotics – both powerful drivers of resistance.

Unfortunately, many of the “gold standard” diagnostic tests that have been used until now are limited by difficult and time-consuming sample preparation, bulky instruments, slow data readout, and low sensitivity and specificity of detection. However, the field of diagnostic technology is growing rapidly and in exciting new directions. Some cutting-edge diagnostic methods sound futuristic and almost fanciful. For example, an infection can be classified as viral or bacterial, and subsequently attributed to a certain pathogen, by measuring the degree of chemiluminescence exhibited by white blood cells in a specially treated sample of whole blood. Signature sequences in bacterial DNA that give away information about its identity and its susceptibility to various drugs can be pinpointed using fluorescently tagged peptide nucleic acid (PNA) constructs. Drug resistant bacteria can even be localized within the body through a simple, noninvasive PET scan by commandeering the proteins that the bacteria normally bind to and tagging them with a radioactive isotope.

Other methods are really extensions of older technology that was conceived decades ago, but is now being overhauled for new applications. Mass spectrometry has been used for 35 years to identify pathogens based on their protein compositions, but its high-throughput sensitivity has only recently been used to distinguish between bacteria of the same family, genus, and even species that are susceptible to different antibiotics. These technologies and others like them give us hope that we can look down the development pipeline not only for new diagnostic tools, but perhaps even for companion novel antibiotic drugs.

One of APUA’s most valuable assets since its inception in 1981 has been its ability to bring together diverse stakeholders in discussion and collaboration. In this issue we probed the front lines of the biotechnology industry to get a sampling of insider perspectives on the opaque world of diagnostic device development. Among our contributors for this Newsletter we have expert epidemiologist Dr. Iruka Okeke’s thoughts on the desperate need for a homogenized diagnostic system in Africa, as well as an opinion article from bioMérieux Inc., a world leader in vitro diagnostics for the past 45 years. We also interviewed research and development experts committed to diagnostic innovation, who are making remarkable advances in the field and that healthcare practitioners everywhere will no doubt keep on their radar.

Diagnosis is the first step. The most innovative and effective treatments, therapies, and miracle drugs can only be put in motion as quickly as the problem can be accurately diagnosed. In the world of infectious disease, delays cause sharp increases in morbidity and mortality. Every wrong prescription makes bacteria more able to evolve into agents that antibiotics may one day be powerless against. APUA and organizations like it will continue working to make sure that day never comes, by promoting infection control, responsible antibiotic stewardship, and incentives for diagnostic innovation. The exploration of new technology and the evolution of diagnosis from slow and misdirecting to immediate and accurate can literally be the pivot point between life and death.

References
The rapid identification of microorganisms has been shown to help guide patient treatment and improve clinical outcome. Waiting several days for a definitive identification of the pathogen provides an obstacle to the clinician seeking to target therapy with the most effective treatment.

If clinicians don’t feel confident in the lab’s ability to deliver quick, accurate results, they are more likely to take a “better safe than sorry” approach, which usually means prescribing a broad spectrum of antibiotics at a dosage high enough to overcome any resistance to a single antibiotic until the susceptibility results are available. In this way, speed of diagnostic laboratory results has a critical impact on curbing the growth of antimicrobial resistance. Now, a new method has emerged that can reduce identification to a few minutes. This speed of results can better guide antimicrobial treatment, helping clinicians to prescribe the right antimicrobial at the right dosage.

Mass Spectrometry (MS) technology has been evolving over the past 50 years. Multiple techniques have emerged utilizing MS that enables rapid and detailed analysis of chemicals, proteins, lipids and DNA. Matrix Assisted Laser Desorption Ionization - Time of Flight (MALDI-TOF) is the technique used for profiling a sample for present proteins. MALDI-TOF has made significant advances in multiple areas especially for cancer and infectious disease biomarkers. In the past decade, MALDI-TOF has been developed for microbial identification using the species specific proteins - or signature proteins - that allow the microbes to be identified at the species level. These molecular “signatures” can be used for rapid bacterial and fungal identification (ID) from isolated colonies.

The introduction of MALDI-TOF for microbial identification transforms the microbiology lab by providing a number of benefits, including organism identification within minutes, higher accuracy than conventional methods, consolidation of testing (bacteria, yeast, fungi, etc.), and significant reduction in the cost per test. The biggest payoff for clinicians is the huge reduction in time that it takes to identify organisms. Specifically, MALDI-TOF enables laboratories to rapidly identify organisms from colonies grown overnight and directly from select patient samples. A process that used to take days can now be limited to hours or even minutes. Once the organism identification is generated, the lab and the clinician have an understanding of the organism type – information that allows for a more targeted therapy.

Integrating the susceptibility testing also provides an opportunity to prescribe only the most effective antibiotics. Equipped with better information, clinicians can avoid empirical prescription, a critical key in reducing the growth of antimicrobial resistance.

Mass Spectrometry: Faster Identification of Microorganisms Points to More Effective Therapies and Good Stewardship of Antibiotics

Nadal Safwat, Ph.D.
Senior U.S. Clinical Marketing Manager
bioMérieux Inc.
platform. This will serve to get more labs using the MALDI-TOF platform to identify microorganisms. The more labs that are able to provide results to clinicians with the speed and accuracy made possible through MS technology, the fewer the cases of antimicrobial misuse.

**Conclusion**

MS technology has the potential to provide a dramatically improved alternative to traditional laboratory identification methods for microorganisms in the process of medical diagnosis. The speed, robustness and minimal costs of sample prep and measurement make this solution ideal for high throughput use. With the speed and accuracy made possible through MS technology, clinicians no longer need to overprescribe antibiotics for patients with infections. By utilizing MS technology, they can quickly discern the type of infection or infections present, allowing them to more specifically target their therapies with the right antimicrobial at the right dosage. Targeted antimicrobial therapy, informed by test results made possible by MS technology and integrated with accurate susceptibility testing, plays an important role in slowing the growth of resistant bacteria.

bioMérieux is a worldwide leader in **in vitro diagnostics for medical and industrial applications. They develop instruments, software, and reagents that are used for healthcare and product safety.**

**From Premonition to Precision: Africa’s Pressing Need for Laboratory Diagnostics and Appropriate Surveillance**

Iruka N. Okeke, Ph.D.  
Associate Professor of Molecular Microbiology  
Haverford College

Ghanaian graduate student Japheth Opintan thought hard and long before he selected his Masters’ thesis project. While not a condition for his program, it was important to him that his project be applicable to healthcare in his country and that it could be completed within a restricted budget. Invasive bacillary diarrhea caused by Shigella was believed to be highly prevalent and having read so much about the global problem of drug resistance, Japheth wondered whether the antimicrobials recommended for treating invasive diarrhea in Ghana were up to the task.

He decided to culture diarrheal specimens and then determine the susceptibility patterns of Shigella isolates. He hypothesized that – as the textbooks say for ‘Africa’ – Shigella would be a principal etiologic agent of diarrhea in Accra, and that he would see resistance to at least some drugs commonly used in Ghana. Given the limited resources in his lab and data from the 1980s available for sample size predictions, he expected to be able to test his hypothesis with under 300 specimens collected within a year, well within the scope of a Master’s thesis research project.

National standard treatment guidelines in Ghana as well as elsewhere in Africa encourage health practitioners to treat bloody diarrheas with orally-active antibiotics that were originally active against Shigella. These typically include trimethoprim-sulphamethoxazole, aminopenicillins and most recently, the fluoroquinolones. Japheth’s study used patient specimens at a teaching hospital in a country where only problematic or refractory cases are likely to be considered for laboratory diagnosis, something that often biases studies towards Shigella isolation.

Nonetheless, the young scientist was in for a surprise: 16 months and 594 carefully-processed specimens later, he had just 24 Shigella isolates. His hypothesis on drug resistance was supported: the paltry Shigella collection was multiply-resistant and he’d localized the resistance genes to plasmids. However, to get even this small number of isolates and complete his dissertation, he had screened more than twice as many specimens as he originally intended.

The astonishing rarity of Shigella in the Opintan et al. study is not likely due to methodological flaws or a temporary drop in Shigella prevalence. Indeed, the only thing odd about it is our collective surprise. The data simply point to other organisms as principal causes of invasive diarrhea in Accra. In a study performed in Western Nigeria in the same decade as Japheth’s, we too isolated Shigella from only 7.1% of stools from patients with diarrhea and 3.6% of controls. We found pathogens that are less frequently sought in Nigeria to be more strongly associated with all and with bloody diarrheas. Shigella has remained common place and relevant at some locations, including some in Africa.

However, the fact of the matter is that even though studies from the 1970s and 1980s reported high rates of Shigella in many West African countries, some parts have seen a decline since then and most parts have seen no surveillance for decades. The evidence base for many national guidelines that recommend valuable drugs like the fluoroquinolones for empirical treatment of invasive diarrhea is insufficient and other syndromic protocols are similarly undersupported.

In the Nigeria study, Shiga-toxin-producing Escherichia coli, for which fluoroquinolones are contraindicated because they increase bacterial toxin production, were three times more...
common than Shigella. Thus, whilst needlessly selecting for quinolone resistance, these drugs could also be harming more patients than they are helping for this specific syndrome.

There is no infectious disease crystal ball. We cannot predict the Shigella prevalence at any locale, nor will we know when epidemiological changes occur, without routine laboratory investigation and surveillance. Similarly, patients should not have to depend on healthworker intuition to be sure that they receive the best available treatments. Clinicians need information about the epidemiology of life-threatening enteric infections in their locality. When they have knowledge about local etiology and susceptibility patterns, patients are more likely to get cost-effective prescriptions at their first visit and selective pressure for drug resistance can be kept as low as possible. And when the first antimicrobial course is unsuccessful, prescribers need microbiology results to guide their next pick. But sadly, necessary laboratory support for managing bloody diarrheas is lacking in most African clinics. Research projects like Japheth’s are similarly uncommon, and far too many prescriptions are based on outdated traditions or unsupported guesses.

The majority of diarrheas should not be treated with antibacterial drugs but bloody diarrhea is sometimes life-threatening and therefore antimicrobials as well as rehydration are recommended in such cases. The more likely that the first prescription is the right one, the less likely that the patient will be harmed, the disease will spread or needless selective pressure for resistance will be high. Culture and susceptibility testing for Shigella and other bacteria is potentially too slow to inform each patient’s therapy but it is critical for identifying outbreaks and providing the surveillance information that makes it possible to respond rationally to future patients’.

The fact that many African hospitals cannot provide this very basic service for bloody diarrheas, life-threatening bloodstream- or even central-nervous system infections is not just problematic, it is unconscionable. And if and when such services are available, clinicians need to be encouraged to use them.

Can the etiologic agents of invasive diarrheas be detected rapidly when the point-of-care is not a district hospital? For some pathogens, microscopic methods and admittedly expensive immunological tests already exist. They are not ideal but are surprisingly cost-effective - now that we urgently need to protect our dwindling antibacterial arsenal – and need to be deployed wherever useful and possible.

Before we rule out testing in the many rural African clinics without laboratories and with budgets that are too constrained to use these tests, we should remind ourselves that there are now commercially available diagnostics that can detect the etiology of calf diarrhea on farms within a few minutes. If tests that can inform treatment can be performed in a muddy field, they can also be used in a village clinic. Although challenging, it is possible to invent and deploy simple but useful tests for curable diseases that afflict so many people in poor countries but which might not have the economic incentive that large-scale agriculture can offer.

Invasive diarrhea is only one example of a potentially deadly syndrome that has multiple possible etiologies, each occasioning a different specific treatment that is threatened by antimicrobial resistance. We need to identify and overcome the roadblocks that stifle diagnostic development, that make drugs that select for expensive resistance problems cheaper to overuse than diagnostics, and the perception that infection-management tools are a luxury rather than a necessity.

Patients and clinicians should have access to diagnostics that are Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free and Deliverable to areas of need (“ASSURED”). Only then will we have the infrastructure to ensure that patients get the best treatment while simultaneously conserving antimicrobials by targeting them to those specific cases where they will be effective.

Japheth A. Opintan is a Microbiology lecturer currently completing his Ph.D. at the University of Ghana Medical School. Dr. Okeke’s book Divining Without Seeds: The Case for Strengthening Laboratory Medicine in Africa was published in March 2011 by Cornell University Press.

References


“If tests that can inform treatment can be performed in a muddy field, they can also be used in a village clinic.”

(Dr. Iruka Okeke)
Next Generation MRSA Screening: an interview with Molecular Detection Inc.

Tzvi Tzubery, Ph.D.
Director of Research and Development
Molecular Detection Inc.

Why is MRSA screening in hospitals important? What is the scope of the problem currently facing healthcare facilities?

Hospital acquired infections (HAIs) are an increasing problem, with infection from the highly contagious MRSA (methicillin-resistant staphylococcus aureus) bacteria among the most prevalent. MRSA bacteria are resistant to all but the most powerful broad-spectrum antibiotics. The Centers for Disease Control (CDC) estimates that in 2008, there were approximately 90,000 persons in the U.S. diagnosed with a MRSA infection, and an estimated 15,000 patients died. Until recently, the incidence of MRSA and MSSA (methicillin-sensitive S. aureus) infections had been rising, but recent evidence suggests that active surveillance (screening) programs, along with other infection control measures, have been effective in reducing MRSA infection rates.

The S. aureus pathogen can be spread by medical personnel, medical instruments, or from exposure to bacteria on furniture or other surfaces. Routine invasive medical procedures create openings for MRSA and MSSA to enter the bloodstream, and hospitalized patients can have weakened immune systems that put them at increased risk. Once a bloodstream infection is established, it can result in serious illness and death, while lengthening hospital stays and increasing medical costs.

What are the costs involved with MRSA and other HAIs?

The costs are high in both human and monetary terms. Researchers have estimated that it costs $3.2 - $4.2 billion annually to treat MRSA in hospitalized patients in the U.S. Duke University researchers estimate that a surgical patient infected with MRSA increases hospital costs by more than $61,000, and a surgical patient with a MSSA infection increases hospital costs by over $24,000. These researchers also found a seven-fold increased risk of death within 90 days for patients who developed MRSA-related surgical site infections as compared to those who did not.

The high costs of these infections are leading healthcare payors to implement financial penalties to provide incentives for achieving better control. Both the Medicare and Medicaid programs have been experimenting with imposing financial penalties on hospitals for above average rates of HAIs and other adverse events. Both programs are already withholding some payments for excessive HAIs and private insurers are instituting similar programs.

How can MRSA screening programs help diminish the infection rate?

Successful MRSA control efforts employ a variety of measures. Among the interventions that are credited with helping to achieve the recent decreases in MRSA infection rates are programs aimed at screening potential carriers. Rapid diagnostic screening to identify carriers of MRSA and MSSA pathogens at the time of patient admission aids in effective control by enabling special precautions to be used with infected patients, their facilities and the personnel who care for them.

A study published in the New England Journal of Medicine earlier this year reported a 62% reduction in MRSA infection rates in ICUs in 153 acute care VA hospitals over a four-year period following the implementation of a “MRSA bundle,” which included universal nasal screening for MRSA.
The National Health Service in the UK has implemented a universal screening policy for MRSA and in June this year reported the lowest-ever level of MRSA infection in its hospitals.

Are new generation diagnostic tests making MRSA screening programs more feasible? More effective?

The MRSA pathogen traditionally has been identified using bacterial culture techniques that require at least two days for results, during which time the bacteria can spread through the facility. A number of molecular diagnostic MRSA assays that provide test results more quickly have become available in recent years, and they have the potential to make MRSA screening far more feasible. A screening test that distinguishes between MRSA, MSSA, methicillin-resistant non-S. aureus pathogens and mixed samples is particularly important for physicians making treatment decisions in the hospital setting, where these infections are most likely to be serious and potentially lethal. We are seeing an increasing number of clinicians at the facilities we serve wanting to know if a patient is at risk for MSSA as well as MRSA. This capacity has also been highlighted by the FDA, which deemed the capability to distinguish MRSA, MSSA and other S. aureus pathogens essential.

Molecular Detection Inc. (MDI) is developing a portfolio of sample-to-answer Detect-Ready® molecular diagnostic tests for the rapid detection of antibiotic-resistant bacteria such as MRSA. The system will incorporate unique technology that analyzes multiple gene targets to produce highly accurate results, minimizing the false positives and false negatives that have limited the utility of some molecular diagnostic assays. Additionally, it can be run on a number of popular diagnostic platforms, affording hospitals maximum flexibility and minimizing the need to invest in expensive equipment.

Molecular Detection Inc. (MDI) is developing and commercializing a portfolio of sample-to-answer Detect-Ready® molecular diagnostic tests for the rapid detection of infectious diseases. MDI recently launched the Detect-Ready MRSA Panel in Europe and Australia for the rapid diagnosis of MRSA and related infections.

Tackling Urgent Needs in Infectious Disease Testing: an interview with Curetis AG

Gerd Lüdke, Ph.D.
Director of Bio-Assay Development
Curetis AG

What led you to focus on the pneumonia application first?

Pneumonia is a high incidence disease with hundreds of thousands of cases each year and a high unmet medical need for more accurate and rapid diagnosis. The disease causes a huge economic burden on healthcare systems and on society at large, with mortality rates of up to 36% and an average hospital stay of 11 to 14 days. Culture-based diagnostics of bacteria and antibiotic resistance is the current gold standard for diagnosis of pneumonia.

However, this typically takes at least two to three days – far too slow. Because of missing diagnostic information most initial pneumonia therapies rely on empiric decisions, which lead to high rates (about 40%) of initially inadequate antibiotic treatments. Inadequate treatment and the widespread use of broad-spectrum antibiotics support the development of antibiotic resistance. Studies have shown that an early adequate and targeted treatment can significantly reduce both mortality and the length of hospital stays. Faster diagnosis could help rule out infection with certain pathogens earlier. In the future this might enable a faster adjustment of antibiotic therapy, and could support other efforts to stop the vicious cycle of rising antibiotic resistance.

Many companies are trying to enter the infectious disease market - what is unique about your company's team approach?

The development of novel diagnostic devices is frequently driven by a “technology-out” approach that does not always focus squarely on clinicians' and users' unmet needs. Many products building on so-called “breakthrough technologies” have fallen short of their great promise. With our cross-functional team of engineers, scientists, physicians, marketing, supply chain and manufacturing experts we have chosen a “market-in” approach instead: our R&D program has been designed to specifically target customer needs by integrating and automating several existing, well-established and proven technologies. The result is a closed, walk-away, easy to use platform (the Unyvero System).

References

which once validated in clinical trials and cleared by the FDA would enable 24/7 testing – not only in microbiology core laboratories but also in near-patient settings.

The Unyvero Pneumonia Application has been designed for the simultaneous detection of 17 pathogens and 22 antibiotic resistance markers at reasonable cost. Producing relevant diagnostic results in three to four hours rather than several days not only helps save patient lives and reduce ICU days, but might also be cost-saving from a hospital's point of view.

What technical challenges did you face in developing your novel applications (the Unyvero platform and Pneumonia Application)?

The Curetis team has learned from extensive global market research studies and key opinion leaders that a new testing solution would have to handle a comprehensive marker panel for bacteria and antibiotic resistances. Such a panel would need to cover more than 90% of all disease-causing bacteria. In the case of pneumonia, epidemiological data from multiple hospitals in the US and Europe has shown that this requires analyzing roughly 40 genetic markers from a single patient sample simultaneously.

This presents a veritable challenge linked to mainly two obstacles: the heterogeneity of the clinical sample types, and the lack of understanding of the predominant antibiotic resistance mechanisms for certain pathogens at a molecular level. During the last four years, we have worked out a truly novel, unique, and rather simple pre-analytics approach to handling all clinically relevant sample types. Our Unyvero Lysator can handle challenging materials, like highly viscous sputa, just as easily as tracheal aspirates, BAL (bronchial alveolar lavage) samples, blood, urine and many others.

For the purposes of analytics, it was also essential to develop an in-depth understanding of the underlying genetics. We have identified what we believe are the best markers for potential antibiotic resistance. However, we will need to carefully demonstrate their clinical relevance in prospective clinical trials for a future FDA filing. Altogether this will require extensive testing of thousands of isolates in clinical trials planned for later this year.

Do you see clinical and regulatory challenges for your products?

The demand to cover not only clinically relevant, but also rare pathogens found in various clinical sample types requires large numbers of patient samples during clinical testing. Such clinical validation is complicated by the fact that microbial culture is a rather poor "gold standard." Peer-reviewed studies have demonstrated the limitations of traditional culture methods. Currently there is no single FDA-cleared platform or assay for highly multiplexed bacteria and antibiotic resistance marker detection available. Therefore we have decided to initiate an extensive, prospective international multi-center clinical trial in Europe and the US to validate our Pneumonia Application’s performance compared to the culture-based standard of care.

However, obtaining regulatory clearance by no means ensures future market success. Users, physicians, hospital administrators and payors demand comprehensive demonstration of product performance and a potential for improving medical and economic outcomes. Clinical trials and development programs focusing on post-marketing trials are essential, but time-consuming and expensive – a challenge for venture-backed companies such as Curetis.

How do you envisage building market-acceptance for your products?

Building acceptance for molecular testing is a challenge that affects healthcare industry, practitioners, and patients. We hope to use expert opinion to increase public awareness and address the gaps in knowledge concerning the importance of rapid pathogen and simultaneous antibiotic resistance marker detection. Every new platform and approach in molecular diagnostics today faces preconceived notions based on the incomplete understanding of infectious diseases and their underlying genetics, and of antibiotics prescription philosophies.

High quality, well-designed clinical studies conducted at centers with reputations of excellence will help convince the broader medical community of the clinical value of any new technology. In this quest, the molecular diagnostics industry needs to work hand-in-hand with societies like APUA towards the common goal of saving patient lives and at the same time reducing healthcare costs by faster, more accurate and comprehensive diagnoses.

Curetis AG (headquartered near Stuttgart, Germany) is a molecular diagnostics company focusing on the development, clinical validation, and commercialization of solutions for easy-to-use, fast, and reliable molecular infectious disease testing.

To date neither the Unyvero Solution nor the Unyvero Pneumonia Application have been validated in clinical trials, nor have they been cleared by the FDA; products are currently not available for sale in the U.S.

### IDSA Recommendations for Addressing Resistance

- Adopt economic incentives and support for other collaborative mechanisms to address the market failure of antibiotics, including establishing new public-private partnerships to strengthen to traditional industry R&D for critically needed antimicrobial drugs.
- Create value-based reimbursement strategies that encourage antibiotic and related diagnostics development.
- Establish a panel of experts to document and regularly revise a list of priority pathogens or infections that have resulted or likely will result in an area of significant unmet medical need, and toward which adopted economic incentives should be targeted.
- Take new regulatory approaches to facilitate antimicrobial development and approval.
- Enhance existing antimicrobial resistance surveillance systems.
- Strengthen activities to prevent and control antimicrobial resistance, including enhancing antimicrobial stewardship.
- Make significant investments in antimicrobial-focused research.
- Boost investment in rapid diagnostics R&D and integration into clinical practice.
- Eliminate non-judicious antibiotic use in animals, plants and marine environments.

(From *Infection Control Today*)
APUA presents study findings to country and global decision makers in Uganda and Zambia

The APUA staff continues to increase dissemination of the findings of the Gates Foundation-supported AR-SANA project in its two target countries. From May 29 to June 11, 2011, Dr. Susan Foster (APUA Director of Public Policy and Education) and Dr. Aníbal Sosa (APUA Director of International Chapter Programs) conducted two country-level workshops and made a series of presentations in Uganda and Zambia. Initial meetings presented findings to the Country Advisory Team (CAT) members, who made many helpful comments and suggestions.

Broader workshops involved health authorities, representatives of health NGOs, and funding organizations. Findings were also presented to Ministry of Health staff, at medical school Grand Rounds, and to medical staff from university teaching hospitals in both countries. Several CAT members and workshop attendees requested access to the outpatient register database, which will be made available.

Special sessions were held at the Centre for Infectious Disease Research in Zambia (CIDRZ; http://www.cidrz.org/), affiliated with the University of Alabama, and the Zambia Center for Applied Health Research and Development (ZCAHRD; http://www.bu.edu/cghd/), affiliated with Boston University. Both research groups found the project findings to be extremely valuable to their ongoing research efforts.

In another venue, an APUA panel on antibiotic resistance was presented at the Global Health Conference held in Washington D.C. on June 14, 2011. Hellen Gelband from the Center for Disease Dynamics, Economics & Policy (CDDEP) spoke on the Global Antibiotic Resistance Partnership (GARP) project activities and Marisabel Sánchez, President of LinksMedia, served as symposium chair. Further dissemination activities are being planned.

APUA renews advocacy to eliminate antibiotics in animal feed in the U.S.

APUA is seeking more scientists to participate in its expanded activities to eliminate misuse of antibiotics in food animal production in the U.S. In the last decade, APUA has published and disseminated a large body of scientific, clinical, and public health evidence to promote more prudent use of antibiotics in food animal production.

In the coming year, it plans further activities to impact public policy by bringing the full weight of science to ensure government accountability in eliminating antibiotic misuse in agriculture. To join APUA’s advocacy campaign, please contact Carol Cogliani (APUA Program Manager) at carol.cogliani@tufts.edu or 617-636-4021.

Recently, two Congressional bills have started to gain traction—the Preservation of Antibiotics for Medical Treatment Act (PAMTA) and the Strategies to Address Antimicrobial Resistance (STAAR) Act. Passage of PAMTA would forbid the use of seven classes of medically important antibiotics for growth promotion purposes, while still allowing their use for treatment of sick animals. The STAAR Act would strengthen the Federal Interagency Task Force on Antimicrobial Resistance (FITFAR) and establish surveillance of antibiotic sales and usage data.

In June 2010, the U.S. Food and Drug Administration also issued a draft guidance, “The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals,” concluding that the use of medically important antimicrobials as growth promoters in food animal production is not beneficial to public health. The FDA recommended that antimicrobial drugs in agriculture should be limited to therapeutic uses with veterinary oversight, and that antibiotics should not be used for enhancing production (i.e. for feed efficiency and growth promotion).

Although this guidance constitutes a step forward in terms of laying the groundwork to build consensus, it falls short. According to Dr. Stuart Levy (APUA Chairman and President), “The fact that the FDA considers mass administration of antibiotics to herds and flocks through feed and water as a viable prevention strategy is cause for concern.” Given the long duration and low dosage of antibiotics given to food animals, heightened antibiotic resistance and other negative impacts on microbial environments are very likely to result. This opinion came from EU experts who observed the effect of the EU ban on antibiotic growth
promoters and testified at the APUA coordinated roundtable in May 2010. Since many animal diseases may be averted by alternative management strategies (e.g. improved animal hygiene, reduced crowding, and “all-in/all-out” housing), public health organizations such as APUA are advocating stronger U.S. regulatory policies to mandate more responsible use of antibiotics by relevant stakeholders (veterinarians, farmers, industry) and to establish a system to monitor and ensure compliance.

**Expert evaluation of the GAIN Act finds it lacking**

In a recent opinion article in *Nature Medicine*, Dr. Paul Ambrose (President of the Institute for Clinical Pharmacodynamics) applauded the initiative taken by supporters of the Generating Antibiotic Incentives Now (GAIN) Act but was of the opinion that “the legislation as written is not likely to have the intended consequences.”

Hospital-acquired infections (HAIs) from antibiotic resistant bacteria have reached an all-time high mortality rate of up to 70,000 deaths per year, and antibiotic resistance has been called the number one threat to global public health by both the WHO and the IDSA. Both organizations have proposed increased surveillance of resistant bacteria, more responsible use of existing antibiotics, and increased incentives to develop new antibiotics.

These initiatives were also recently reintroduced to Congress (after failing to pass in September 2010) by Georgia representative and physician Phil Gingrey in the form of the GAIN Act. The legislation would grant faster application reviews from the FDA for newly developed drugs, and if licensed, would extend marketing exclusivity of those drugs to ten years (from the current five).

However, Dr. Ambrose points out why the GAIN Act may not be enough to revitalize the antibiotic pipeline. First, the legislation only provides for an experimental drug. More importantly, the GAIN Act alone simply does not provide sufficient medical reimbursement for the research and development of a new drug. The current price for antibiotic drugs, compared to lifestyle drugs or treatments against chronic illness, is simply too low to provide incentive to invest in this very expensive process. As proof of both these allegations, Dr. Ambrose notes that many pharmaceutical companies in the U.S. and in Europe (including the world’s two largest – Pfizer and Johnson & Johnson), have already dropped antibiotic development from their research roster within 2011 despite impending reintroduction of the GAIN Act. There is even less incentive for the smaller, usually venture capital-funded, biotech companies.

In addition to the GAIN Act, Dr. Ambrose urges legislators and the healthcare industry to simplify the path to regulatory approval for experimental drugs and to provide more investment incentives to pharmaceutical companies, such as greater protection for intellectual property, R&D tax credits, research subsidies, and tax relief for educational programs that promote prudent antibiotic use. APUA is following this legislation with the objectives of increasing incentives for development of novel agents while promoting more prudent use of antibiotics once they are on the market.

“We need to work on both ends of the equation to be able to have access to cost-effective antibiotics,” says Kathleen Young (APUA Executive Director).


**APUA poster on African research at the 49th Annual Meeting of the IDSA**

The 49th Annual Meeting of the Infectious Disease Society of America (IDSA) and the HIV Medicine Association will be held in Boston, Massachusetts on October 20-23, 2011. APUA will present a poster titled “Antibiotic resistance compromises treatment of pneumonia in Ugandan children,” showcasing Gates Foundation-supported research done by Dr. Susan Foster (APUA Director of Public Policy and Education), Dr. Anibal Sosa (APUA Director of International Chapter Programs), and Dorothy Ochieng (APUA Project Manager).

The project documented the rising occurrence, treatment, and impact of antibiotic resistance in the treatment of acute respiratory infections in Ugandan children under the age of 6. Project findings suggest that antibiotic therapy was often ineffective or absent, contributing to antibiotic resistance levels of almost 80% to the most commonly prescribed antibiotic, cotrimoxazole. The goal of this and other IDSA presentations is to increase awareness of rising levels of antibiotic resistance, and the global need for alternative antibiotics.

**EU-U.S. workshop on the need for diagnostics to combat antimicrobial resistance**

The U.S. and EU members of the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) have called for a workshop on “Challenges and Solutions in the Development of New Diagnostic Tests to Combat Antimicrobial Resistance,” to be held in Brussels, Belgium on September 28-29, 2011. The workshop aims to recognize the potential of rapid diagnostic tests to guide and enable faster initiation of narrow-spectrum antimicrobial therapy, and to identify the factors that hinder the development, approval, introduction, and appropriate use of novel antimicrobials and new diagnostic tools.

Dr. Donald Low (Chief of Microbiology, Mount Sinai Hospital, and member of the APUA Scientific Advisory Board) will introduce the keynote session and speak on “Setting the Stage: Significance and Need for Rapid Diagnostic Tests for Invasive Bacterial Infections.” Dr. Rosanna Peeling (Professor and Chair of Diagnostic Research, London School of Hygiene and Tropical Medicine) will follow with “A Review of Candidate Technologies,” and Dr. John Rex (Associate Professor of Medicine, University of Texas) will address “The Importance of Rapid Diagnostics for Advancing Antibacterial
APUA Activity and Related Events

Four subsequent sessions and panel discussions will focus on 1) technical and scientific challenges in the development of rapid diagnostic tests, 2) regulatory challenges, 3) economic factors, and 4) challenges in the acceptance and adoption of new diagnostic tests. For more information, please contact Dr. Jane Knisely (Program Officer, DHHS/NIH/NIAID) at Jane.Knisely@nih.gov or Rachida Ghalouci (Project Officer, European Commission) at Rachida.Ghalouci@ec.europa.eu.

APUA and Massachusetts Department of Public Health sponsor antibiotic stewardship educational program

The Massachusetts Department of Public Health and Massachusetts Coalition for the Prevention of Medical Errors, in association with Tufts Medical Center, UMass Memorial Medical Center, Brigham and Women’s Hospital, and APUA, will sponsor an educational program on “Building Stewardship: A Team Approach” in Shrewsbury, Massachusetts on September 14, 2011 (with pre- and post-session audioconferences to be held in September and November).

The program will focus on implementing and optimizing antibiotic stewardship in acute care hospitals, enhancing patient care and safety, and reducing antibiotic resistance and societal cost. Physicians, nurses, pharmacists, microbiologists, administrators in acute care facilities, and other experts will participate in the program as multi-disciplinary teams.

Dr. Kenneth Lawrence (Assistant Professor of Medicine, Tufts University) will speak on “Strategies for Stewardship and Tools for Implementation,” followed by Dr. Kristi Kuper (Cardinal Health Pharmacy Solutions) on “Building a Stewardship Program” and a panel discussion on best practices. Group sessions with experts will focus on problem pathogens, business plans, evaluation and IT metrics, and hospital team planning. Register here or visit the Massachusetts Coalition for the Prevention of Medical Errors website for more information.

FDA workshop on antibacterial drugs for the treatment of acute otitis media (AOM)

The FDA will sponsor a workshop on “Issues in the Design of Clinical Trials for Systemic Antibacterial Drugs for the Treatment of Acute Otitis Media” in Silver Spring, Maryland on September 7, 2011. The objective of the three-session workshop will be to discuss scientific issues in the design of clinical trials of antibacterial drugs for the treatment of AOM (middle ear infection), including appropriate endpoints, the role and effect of tympanocentesis (drainage of fluid from the middle chamber of the ear), the feasibility and acceptability of superiority trial designs, and available data that might support feasible non-inferiority trial designs.

Session 1 will provide a review of current guidelines for clinical care of AOM, previously conducted clinical trials, FDA draft guidance for industry, and regulatory and ethical considerations. Session 2 will discuss recently conducted placebo-controlled clinical trials of AOM, and Session 3 will discuss clinical endpoints and scientifically supported feasible trial designs.

The workshop will be held in the Crowne Plaza Hotel at 8777 Georgia Avenue in Silver Spring, Maryland. For more information see the notice on the Federal Register.

Gates Foundation accepting grant proposals for Grand Challenges Explorations

The Bill & Melinda Gates Foundation is now accepting grant proposals for Round 8 of Grand Challenges Explorations, an initiative to encourage innovative and unconventional global health and development solutions. Applicants can be at any experience level; in any discipline; and from any organization.

Grant proposals are being accepted online until November 17, 2011 on the following topics: 1) Protect crop plants from biotic stresses from field to market, 2) Design new approaches to optimize immunization systems, 3) Explore new solutions in global health priority areas, 4) Explore nutrition for healthy growth of infants and children, and 5) Apply synthetic biology to global health challenges.

Initial grants will be US $100,000 each, and projects showing promise will have the opportunity to receive additional funding of up to US $1 million. Full descriptions of the new topics and application instructions are available at: www.grandchallenges.org/r8_gce.