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Antibiotic Stewardship Programs: Proven Strategies to Preserve Medicine's "Magic Bullets"

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The development and widespread use of antimicrobial agents has been among the most important public health interventions in the last century.[1] Yet these "magic bullets" may fall victim to their own success if the development of resistance continues at its current pace. Antimicrobial stewardship programs attempt to balance the demand for these life-saving drugs with the need to preserve their future efficacy. Effective antimicrobial stewardship employs both knowledge of patient-level and ecologic effects of antimicrobials as well as the psychology of human behavior change.

Strategies to influence prescribing patterns and improve antimicrobial use can be broadly divided into three approaches: educate the prescriber to make the "correct" choice at the time of prescribing (education and guideline strategies); review antibiotic prescribing after the fact and attempt to persuade prescribers to change undesirable prescriptions (review and feedback strategies); and control prescribing options by dictating which antibiotics a clinician may or may not prescribe (formulary and restriction strategies and antibiotic cycling strategies) (Figure 1). A number of comprehensive reviews have examined the subject in great detail[2-4]; here I would like to address two questions driving some of today's most innovative approaches to antimicrobial stewardship.

Are some antibiotics more likely than others to promote resistance?

A frequently employed strategy in antimicrobial stewardship programs is the explicit control of what antimicrobials may be used (as in antimicrobial cycling) or not used (antimicrobial restriction) in a given situation. Antimicrobial cycling is a concept analogous to crop rotation, where during a certain time period one particular antimicrobial is used to the exclusion of all others (e.g., cefepime one month, imipenem the next month, etc.). In antimicrobial restriction, certain antibiotics are not available for use without prior approval.

Both of these strategies enable a high degree of influence over antimicrobial prescribing, but the question is: which antimicrobials should we use or not use? Historically, agents have been targeted

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Hygiene for the Healthy Household: APUA Launches Project Aimed at Consumers

A new APUA initiative, funded by an unrestricted educational grant from The Clorox Company, will address rational hygiene practice in the home and community. With increasing resistance to antimicrobials, effective hygiene has become an essential tool in preventing infection and reducing subsequent demand for antimicrobial agents. Saturation of the market with hundreds of antibacterial products has led to confusion among consumers. Urgently needed is trustworthy advice on household cleaning purchases and product use. Yet there has been little scientific research defining "responsible hygiene" for individuals and

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APUA One-on-One

Moxifloxacin: New TB Miracle Drug?

Interview with Richard Chaisson, M.D.
Director, Center for TB Research
Johns Hopkins University

In late 2005, the Global Alliance for TB Drug Development, in collaboration with Bayer Healthcare AG, announced it would study the effectiveness of the antibiotic moxifloxacin for tuberculosis. Dr. Richard Chaisson, leading two international efforts, will assess the ability of the drug to shorten the period required to cure the disease – from six months to three or four months. Each year, TB kills more than two million victims worldwide.

Q: Why did Bayer decide to undertake these trials?

A: The simple answer is: They saw that the studies were going to happen, one way or another. And because the Global Alliance for TB Drug Development was interested in and willing to pursue a partnership with them, it was feasible for them to be involved.

Q: If this treatment works, what will it mean for the rest of the moxifloxacin

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Letter to the Editor:

The Case for Conservation: Antimicrobials as a Natural Resource

In 2006, a natural resource, almost as indispensable to human life as clean air and water, is both under serious threat and frequently excluded from the public discourse on environmental protection. Antibiotics, and more broadly antimicrobial drugs, are a natural resource because they are biomimetic, patterned after living organisms and organic substances. When this resource is used indiscriminately, it pollutes a pristine equilibrium, one achieved through millions of years of competition between microbes. The application of the environmental protection framework is therefore appropriate.

An environmental protection initiative for conserving microbial resources would require a codified, international approach. The "polluter pays" principle would permit civil proceedings in the International Court of Justice against nations abusing antimicrobials. China's admission of amantadine use, approved only for human treatment, in its poultry flocks would have been actionable under such a regime. Paying damages to drug companies may seem like a small price for having flirted with an avian flu pandemic, but if agriculture authorities knew they risked landing their nation in court, they might hesitate to treat livestock, worth a few thousand dollars, with a multimillion dollar antimicrobial. In politics, a dose of transparency is always the best medicine.

Andrew Romaner
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for restriction based on their higher costs relative to similar therapies. However, with greater understanding of the relationship between antimicrobial use and resistance, the restriction of antimicrobials in order to influence antimicrobial resistance patterns has become a primary area of investigation.[5]

The classic example of the effect of antimicrobial restriction is the study by Rahal et al.; in response to an outbreak of extended-spectrum beta-lactamase-(ESBL)-producing *Klebsiella*, a hospital instituted strict restrictions on all cephalosporin use.[6] Subsequently, the incidence of resistant *Klebsiella* decreased significantly. However, due to an increase in use of imipenem/cilastatin, the incidence of imipenem-resistant *Pseudomonas aeruginosa* increased.

This phenomenon has been referred to as "squeezing the balloon"; changing from the use of one agent to another may reduce resistance to the first drug, but increase resistance to the second.[7] A goal in restriction-based strategies is to avoid substituting one resistance problem for another. While virtually all antimicrobials apply selection pressure, might some "squeeze the balloon" more lightly than others?

Recently, there has been a trend towards restricting cephalosporin usage and increasing utilization of β-lactamase inhibitor combinations (such as piperacillin-tazobactam and ampicillin-sulbactam). This approach has been supported by studies demonstrating a protective effect of piperacillin-tazobactam against infection by ESBL-producing organisms and VRE (vancomycin-resistant enterococcus), in comparison to cephalosporin administration.[8, 9]

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APUA's research and educational projects are made possible through the generous support of private donations, government grants and individual memberships, as well as unrestricted grants from corporate contributors. APUA programs promote the prudent use of existing antimicrobials, as well as development of innovative products, diagnostics, antimicrobials, and vaccines. We are grateful to all of our corporate and project partners listed and welcome other collaborations to control antibiotic resistance and improve antibiotic treatment in the industrial and developing world. APUA Project Partners include: American College of Physicians - American Society of Internal Medicine, Cambridge, Massachusetts Schools, Centers for Disease Control and Prevention, Coalition for Affordable Quality Healthcare, Chiron Foundation, the Grodzins Fund, U.S. Food and Drug Administration, International Society for Infectious Diseases, Izumi Foundation, the Joyce Foundation, Management Sciences for Health, Massachusetts Department of Public Health, Massachusetts Medical Society, Merck Research Laboratories, the Nathan Cummings Foundation, National Institute for Allergies and Infectious Diseases, Nurse Practitioner Associates for Continuing Education, Pan American Health Organization, Pan American Society for Infectious Diseases, Tufts Health Care Institute, U.S. Agency for International Development, U.S. Department of Agriculture, University of Illinois, the Wellcome Trust, World Bank, World Health Organization, and other foundations. APUA gratefully acknowledges unrestricted corporate contributions from: Aetna Healthcare; Alcon Labs; AstraZeneca; Bayer Healthcare AG; A.B. Biodisk; Biomérieux; Bristol Myers Squibb; The Clorox Company; Cubist Pharmaceuticals; GlaxoSmithKline; Ortho-McNeil Pharmaceutical; Paratek Pharmaceuticals; Wyeth Pharmaceuticals.

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Landman et al. restricted the use of third-generation cephalosporins, vancomycin, and clindamycin in their institution and encouraged use of piperacillin-tazobactam and ampicillin-sulbactam.[10] Analysis of monthly incidence rates of resistant pathogens reported a significant decrease in isolation of methicillin-resistant *Staphylococcus aureus* as well as ceftazidime-resistant *Klebsiella*, although the proportion of resistant *Acinetobacter* isolates increased. Other hospitals have also observed a decrease in ESBL-producing organisms after adding piperacillin-tazobactam and restricting ceftazidime.[11,12] Studies have also documented reductions in the rates of VRE and *Clostridium difficile* after restriction of cephalosporins and "replacement" with β-lactamase inhibitors [13-16], although this has not been seen in all studies.[17] Future studies validating (or invalidating) these data on the relative potential for antimicrobials to contribute to resistance on a hospital-level scale may help guide the future of antimicrobial restriction strategies.

How can technology enhance antimicrobial stewardship programs?

The increasing computerization of the hospital environment offers new opportunities for programs to optimize antimicrobial use. These opportunities have primarily been associated with implementation of computerized physician order-entry systems in hospitals. The order-entry encounter can enhance each of the antimicrobial stewardship strategies shown in Figure 1. Facilitation of educational interventions may be as simple as a link to the institution's guidelines for therapy, or as sophisticated as computerized expert systems that integrate patient-specific laboratory and microbiology data in devising a suggested therapeutic regimen. If a prescriber enters an order for a restricted agent, a list of formulary alternatives can be suggested, along with the pager number needed to obtain authorization. When an agent targeted for review is ordered, the data can be forwarded in real time or entered into a queue for later review by antimicrobial stewardship personnel.

The most advanced programs integrate patient-specific data extracted from hospital information systems to provide tailored recommendations for therapy using rules-based criteria ("expert systems"). The choice of antimicrobial is guided by the results of the patient's cultures (for definitive therapy) or by hospital-specific resistance patterns (for empiric therapy). Information on the patient's height, weight, and renal function is incorporated in determining dosing recommendations, and contraindications such as allergies are automatically checked.

The group at the Latter-Day Saints Hospital in Utah has authored a number of studies on the use of their expert system decision-support tool for antimicrobial selection.[18,19] One study examined the effect of the introduction of the program into a 12-bed intensive care unit over a 12-month period.[20] The program was integrated into the medical-information system and provided recommendations for therapy; physicians were not required to follow the recommendations but had to provide rationale for their choice if they ordered a non-recommended antimicrobial.

In approximately half of all courses of therapy the physician followed the computer's recommendations. Compared to the two-year preintervention period, in the intervention period fewer antimicrobials were used, the mean cost of antimicrobials decreased, fewer antimicrobial-related adverse drug events occurred, and fewer patients were treated with a drug to which their infecting organism was not susceptible. Moreover, within the intervention period, outcomes were improved if the physician followed the computer's suggested regimen rather than overriding the computer. Thus, the integration of advanced information technology into antimicrobial stewardship programs holds the potential to both reduce antimicrobial overuse and improve outcomes, benefiting both the patient being treated and future patients relying on the effectiveness of our antimicrobial armamentarium.

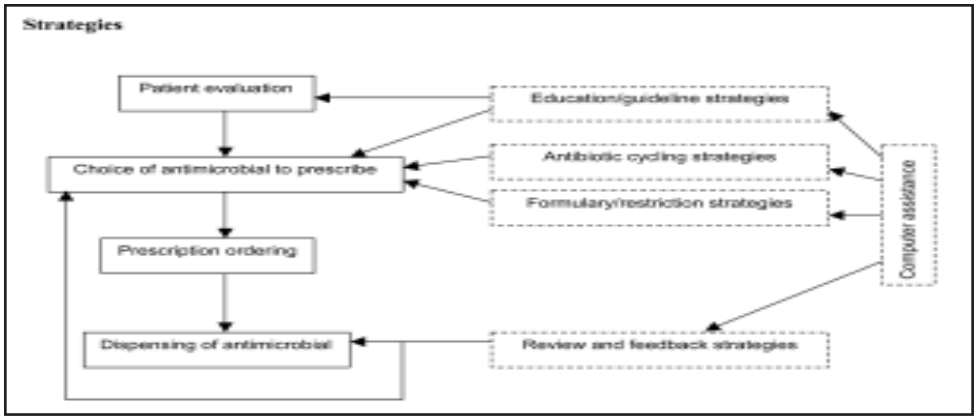

Figure 1: Antimicrobial Prescribing Process and Antimicrobial Stewardship Strategies (adapted from ref. 2)

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Will Antibiotics Become Useless by 2015? A UK Forum Debates

The first meeting of the 2015 Forum, a debating society chaired by the APUA-UK's Peter Davey, recently debated the statement: "This House Believes That By 2015 All Antibiotics Will Be Redundant." What follows are highlights from the discussion, as summarized by freelance medical journalist Jenny Bryan.

At the inaugural debate, 2015 Forum chairman, Professor Peter Davey (Director of the Health Informatics Centre, University of Dundee), pointed out that all antibiotics are already ineffective for some patients with vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-resistant *Staphylococcus aureus* (GRSA), *Acinetobacter* spp, *Mycobacterium* tuberculosis, and atypical mycobacteria. "The fuse is lit, and unlike most fuses that burn at a constant rate, this one is accelerating," he argued, in his opening address in support of the motion.

For example, between 1992 and 2002, MRSA rates in British ICUs rose from less than 10% to 50%, and levels are likely to rise still further, predicted Professor Davey. By 1997, MRSA prevalence in ICUs in France, Italy and Greece had already exceeded 75%. Meanwhile, data from the European Antimicrobial Resistance Surveillance System (EARSS) show increasing quinolone resistance in 16 of 21 countries, with VRE rates over 10% in five countries, and penicillin-resistant *S. pneumoniae* (PRSP) rates over 25% in five countries, and over 50% in France.

Professor Davey was further pessimistic about the prospects for more effective treatments for bacterial infection by 2015. While 11 new classes of antibiotics were developed in the first 30 years of the antibiotic era, he told 2015 Forum members, this dropped to just two new classes in the last 30 years. "The rising cost of developing new drugs and, in the case of novel antiinfective agents, the relatively low financial return compared to drugs for CNS and some other diseases have contributed to the dearth of innovative antibiotics," Davey explained.

Seconding the motion, Dr. Alison Holmes (Hammersmith Hospital, London) argued that if antibiotics are not to become useless by 2015, the drugs must be restricted and better infection control procedures implemented. "If we do want to be using antibiotics in 2015, we need to stop using antibiotics in hospital-acquired infections, and we need to ban them in dialysis units," said Dr Holmes. "We're already discussing rationing of flu vaccines and drugs, and we should do the same for antibiotics."

Not all doom and gloom

In contrast to the ominous warnings of the proposers of the motion, Professors Roger Finch (University of Nottingham) and Peter Hawkey (University of Birmingham and Health Protection Agency) presented a more optimistic view of the bacterial environment in 2015.

"Antibiotic resistance is a threat that we need to accept, but this is not a time for negative thinking. Recognition of resistance as an important healthcare challenge by physicians, politicians and patients is leading to sustained efforts and a multifactorial strategy for its control," said Finch. He pointed out that, although resistance levels are rising, the proportion of patients who fail antibiotic treatment because of resistance remains a small fraction of those who benefit.

Professor Finch also dismissed the idea that there would be no innovative approaches to bacterial infection over the next ten years as "incompatible with the nature of mankind." Focusing on the dozens of antibiotics introduced in the 1970s-1990s, Finch noted that though they may have been based on innovative predecessors, they had nonetheless made essential contributions to overcoming resistance. Hawkey reminded the audience that antibiotic resistance can fall, as demonstrated by the renewed activity of tetracyclines in the management of acute exacerbations of chronic bronchitis. Finch predicted that physicians would start to see the fruits of genomic research over the next five years, with 25 new agents expected by the end of the decade.

In the subsequent discussion, Professor John Primrose (Southampton General Hospital) supported the more optimistic approach of those opposing the motion, and felt that genomic research would yield useful products. Professor Mervyn Singer (University College Hospital, London) was disappointed that opposers of the motion hadn't mentioned the potential of antimicrobial peptides, and the possibility of nanotechnology.

However, Mr. James Wellwood (Whipps Cross Hospital, London) observed that before he stopped using antibiotics in surgery, he would need clear evidence to show that they weren't necessary — otherwise, he would be in danger of being sued. "If I've got a septic patient, should I take a gamble and say that I'm not going to treat because I don't want resistance? It's a bit tough for the patient, if he deteriorates too far, and I can't get him back!" Summing up his case, Professor Davey explained that he wasn't advocating not treating septic patients, but urged more effort to define patient need in terms of their capacity to benefit from treatment.

Professor Finch advocated greater patient involvement before decisions are made to ban antibiotics: "No one has asked the patients, and we need to start asking them, and involving them in decision-making," he said. "Maybe we should also be using the newer drugs earlier, instead of flogging the old antibiotics."

Final vote

4 in favor of the motion.
5 against.

Motion failed.

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market? Will use be restricted for TB?

A: It's hard to know at this point. The fear among Bayer and other companies that make fluoroquinolones is that if their drug is seen as being good for TB, then that will restrict its use in other indications. Is it possible that at some point in the future the global infectious disease community will say, 'Fluoroquinolones should be reserved for tuberculosis'? I actually can't imagine that. Fluoroquinolones are so important, and have such broad usage, that to say we're going to restrict them for TB is unimaginable. I'm right now attending on our inpatient HIV service, and I can tell you half the patients are on a fluoroquinolone. I can't imagine not being able to use fluoroquinolones for our community-acquired pneumonia patients, our patients with enteric infections, or for diabetic foot infections. So I just don't think it's going to happen that way. But I understand the companies are concerned about it.

Q: Is there any credible rationale for restricting moxifloxacin to TB patients?

A: What if moxifloxacin turns out to be the most incredible drug for TB — one that will shorten the duration of therapy down to three months? It could have a major impact on tuberculosis control worldwide. If moxifloxacin or other quinolones are used in patients who happen to have TB, but aren't being treated for it because their physician doesn't know they're infected, and they develop resistance, there's a real concern. People will say, 'We shouldn't use quinolones for any other indication, because they might promote resistance in TB.'

Q: Moxifloxacin is used widely in respiratory and skin infections. If it becomes widely used for TB, what are the chances of cross-resistance?

A: The likelihood of cross-resistance, quinolone to quinolone, is essentially 100%. If you're resistant to quinolones, you're resistant to the class. Is that absolutely true? Well, probably not. But it's true enough for practical purposes.

Q: So will this endanger other uses of moxifloxacin?

A: The use of moxifloxacin for treating TB is not going to endanger the treatment of other infections. I honestly don't think that that's where you're going to see the development of resistance. Where you see the development of resistance is with short term use of quinolones. The resistance that has emerged has been somewhat of a surprise. For instance, we're seeing the emergence of quinolone-resistant gonorrhea in association with the use of Cipro® or ofloxacin, for the treatment of multiple infections. With broad use of those drugs, there's been the emergence of gonococcal isolates that are quinolone resistant. Treatment with a very potent quinolone for a long period of time in a fairly narrowly defined patient population: I don't think this is going to result in the emergence of resistance in gonorrhea or pneumococcal infections.

Fluoroquinolones are so important, and have such broad usage, that to say we're going to restrict them for TB is unimaginable.

Q: Do you foresee any dangers from widespread moxifloxacin use?

A: The major worry that I have is that broad and indiscriminate use of quinolones might lead to TB that's resistant to quinolones. And then moxi won't work.

Q: What proportion of people in the world who need TB treatment is actually treated?

A: If you look at the WHO data on treatment under DOTS programs, it's under half. So more than half of the patients in the world either don't get treated at all, or don't get treated in programs that treat them properly.

Q: So could moxifloxacin save lives if it increases compliance — therefore preventing relapse and drug resistance?

A: If you have a regimen that could be more easily completed, then it saves lives by helping more people get treated. It saves lives by preventing treatment failure from non-compliance. And hopefully prevents the emergence of resistant TB.

Q: At least 12 million people around the world are infected with both HIV and TB. How would the moxifloxacin trials affect the AIDS epidemic?

A: It doesn't affect AIDS directly. TB is one of the leading causes of death in people with HIV. So if you have a better treatment for people who are at high risk of dying from TB, then that's going to reduce mortality from TB. It won't have an effect on overall AIDS mortality or HIV transmission. HIV impairs the immune system, and the immune system is what controls TB — so if you have HIV and you're also infected with TB, you're much more likely to get sick. But having TB doesn't increase your risk of getting HIV. Having HIV doesn't increase your risk of getting infected with TB, but it does increase your risk of getting sick with TB if you are infected.

Q: It always seemed that of today's three horrific pandemics today — AIDS, TB, and malaria — that TB could have been the easiest to contain if resources and consciousness had been trained that way. Do you agree?

A: Yes. The tools that we need to control TB have been available for a long time. If we had used them well, things would be much better than they are. But we haven't used them well.

Q: Is moxifloxacin a possible turning point?

A: In terms of progress with drug development, the prospects are better now than they have been for a long time.

Dr. Chaisson spoke with Associate Editor Madeline Drexler.

Birth of a Public Surveillance System: PAHO Combats the Spread of Antimicrobial Resistance in Latin America

By Gabriel Schmunis and
Roxane Salvatierra Gonzalez

The Pan American Health Organization (PAHO) has many partners in containing antimicrobial resistance: 19 Latin American countries; the United States Agency for International Development (USAID); the Government of Canada; the United States Centers for Disease Control and Prevention (CDC); the Alliance for the Prudent Use of Antibiotics, and the American Society for Microbiology. Of these, the most critical partners are the countries themselves, since it is at the national level that most activities and investments take place.

The countries of the Region of the Americas and PAHO have a mandate from the Ministries of Health, who in 1995 established an Expert Committee on emerging diseases with specific goals and objectives for the countries to meet.[1] Another mandate arises from the implementation of the WHO Global Strategy for Containment of Antimicrobial Resistance.[2,3] Both of these mandates propose objectives to be met by countries in regard to antimicrobial resistance (AMR). The Technical Advisory Group that leads PAHO's activities on the subject narrowed these objectives[4-6] to focus on: 1) advocacy to prevent and control antimicrobial resistance; 2) surveillance to provide evidence of the existence and magnitude of such a threat; 3) estimates of AMR-related costs; and 4) interventions to contain the spread of resistance and limit the use of antibiotics, while simultaneously helping to control the costs of treatment using model clinical guidelines and a formulary to be developed and adapted to countries of the Region.

Surveillance strategy

Surveillance of AMR was based on routine laboratory data and strengthening the laboratory capability through training of laboratory personnel.[7-10] In order for the system to work, each country was required to select a coordinating laboratory, the National Reference Laboratory (NRL), and a network of national sentinel laboratories (NSL). As a general rule, the national public health laboratory in each country was selected as the reference lab. The exception was Ecuador, where the network is coordinated by a private hospital's microbiology laboratory of recognized excellence.

The national reference laboratories participate in a performance evaluation program by receiving unknown isolates for identification and antimicrobial susceptibility testing.[7-10] National reference laboratories supervise the national network to make sure that norms and regulations are followed; act as a reference center; conduct periodic performance evaluation of national sentinel laboratories; and consolidate data on antimicrobial susceptibility testing received periodically from national network participants. In turn, sentinel laboratories identify species of bacteria; conduct antimicrobial susceptibility testing; and disseminate results locally. Norms for standardization of performance evaluation for antimicrobial susceptibility testing, either by Kirby Bauer[11] or automated techniques,[12] were developed by expert committees organized by PAHO.

Surveillance of resistance of enteric pathogens began in late 1996, with identification and susceptibility testing of *Salmonella, Shigella,* and *Vibrio cholerae* isolates. These three species were important in the Americas from epidemiologic, economic, and political perspectives. Strains of *Salmonella* and *Shigella* were known to be partially responsible for diarrhea in children, a condition that kills thousands of children under five years of age in the Americas. Outbreaks of shigellosis strike victims of any age; even when there are no case fatalities, these outbreaks hurt countries at least partially dependent on tourist income (e.g., countries in Central America and the Caribbean).

Given the development of common trade markets within the Region, commerce of farm and agricultural products increased exponentially in the 1990s. Foodborne diseases economically hurt countries when agricultural or farm produce becomes contaminated.

Cholera reappeared in the Americas in 1991 after 90 years of absence. In 1996, cholera was still spreading in the north of South America and in Central America, where it remained a problem until early in the new decade. Between 1996 and 1999, three subregional workshops for enteric pathogens were conducted to standardize techniques for microorganism identification, antimicrobial susceptibility testing, quality assurance, and performance. The training was aimed at having all national reference laboratories speak the same language.

From 1999 to 2000, six countries expanded the number of species under surveillance. Five of them were already conducting surveillance of *Streptococcus pneumoniae* two years earlier. From 2000 to 2004, 11 national workshops were held on standardization of techniques for bacterial identification, antimicrobial susceptibility testing, quality assurance, and performance evaluation on enteric and other species of microorganisms. Regionally, three courses were conducted on biosafety, two on WHONET, and three on shipment of strains following IATA regulations. Personnel from 13 countries have been trained and are authorized to sign forms required by IATA for shipment of isolates.

Surveillance, which began with eight countries in 1996 (Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico, Peru and Venezuela), was later expanded to five Caribbean countries. Finally, in 1999, the group expanded to 20 countries with the addition of Bolivia, Cuba, Ecuador, El Salvador, Guatemala, Nicaragua, and Paraguay. Except for Cuba, no country in the latter group had any organized system for routine surveillance for bacteria species at that time.

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On the other hand, countries with experience in surveillance have shown improvement. The Mexican National Reference Laboratory reported results on AMR for 163 *Salmonella* isolates in 1996. Obviously, these data did not reflect the full scope of the threat in that country. The number of isolates increased significantly over time, and reached 1779 in 1999.[13] By 1998, Latin American countries had a good map of the resistance of *Vibrio cholerae* (Figure 1), as well as of *Salmonella* and *Shigella*.[13] Further improvement was achieved in subsequent years. By 1999, in Nicaragua, 100% of *V. cholerae* isolates were determined to be resistant to tetracycline, ampicillin, and trimethoprim/sulfamethoxazole, but still susceptible to erythromycin. Resistance profiles for *Salmonella* and *Shigella* were available for Bolivia, Ecuador and Paraguay, three countries that had never obtained this information before as part of an organized national surveillance system.

More recently, national surveillance systems identified *Salmonella* serovars. By 2000, the Latin American Network for Antimicrobial Resistance Surveillance *(Red Latinoamericana de Vigilancia de la Resistencia a los Antibióticos {ReLAVRA})* was functioning.[7] Through the network activities[7-10], information on resistance was available on enterics as well as on other species (Table 1). With this foundation, it was relatively easy to incorporate other stakeholders (infectious diseases specialists, nurses, midwifes, infection control professionals) into the crusade to combat AMR.

Canada and the US had no autochthonous cholera. Bolivia, Chile, Costa Rica, Ecuador, Guyana, Panama, Paraguay, Suriname and Uruguay, no information. From all other countries, isolates were resistant to tetracycline and/or trimethoprim-sulfamethoxazole, erythromycin and ampicillin. In Venezuela, resistance was to ampicillin only.

A few countries, like Brazil and Colombia, began to report antimicrobial resistance for *Salmonella* discriminating by the origin of the isolates in 2002.[9] Mexico began in 2003.[10]

By 2002, 12 countries had expanded surveillance to other species,[9] although not all countries conduct surveillance of all the recommended species. Sixteen countries reported the species under surveillance from isolates obtained both in hospitals and the community, and the number of isolates tested in 2003 (See Table 2 on p. 8).[10]

Most species currently under surveillance were not part of an organized national surveillance system prior to 1999. In 2003, 426 sentinel laboratories participated in the network; 167 of them conducted surveillance of enteric pathogens only. PAHO receives from the national reference laboratory of each participating country consolidated results of thousands (130,000 in 2003) of isolates tested[10], from *Streptococcus pneumoniae, Shigella* and *Acinetobacter* to methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.[7-10]

Although these consolidated results are of limited epidemiologic value, they are useful to show trends of AMR through time, and for advocacy. When national reference laboratories from each country consolidate the results for each species, they also have the AMR pattern for the various sentinel sites, and can monitor whether these results are available to hospitals. This helps determine whether treatment guidelines agree with the resistance profiles of the bacterial isolates in that setting.

Figure 1. Countries with resistant *Vibrio cholerae*, 1998 (dark gray).

PAHO also tries to determine national performance through evaluation visits. For this purpose, guidelines were developed for the evaluation of a surveillance system for emerging diseases, including AMR. Evaluations of the national reference laboratory for AMR surveillance have been conducted in Argentina, Bolivia, Brazil, Chile, Costa Rica, Ecuador, Paraguay, Peru, Uruguay and Venezuela. Only one NRL was found to be substandard. Evaluations of 55 sentinel sites in ten countries further indicated shortcomings, generating doubts about the credibility of their results. These shortcomings underscore why national reference laboratories may act as national sentinel sites by processing thousands of isolates annually. While the results of surveillance are believable, the same results are doubtful when applied to patient care, because sentinel sites may not follow one or more quality assurance norms.

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Table 1. *Streptococcus pneumoniae:* % resistant strains, 2003

Country		% of resistant isolates (all ages)						
	Number of strains	OXA*	PEN	VAN	ERI	OFX	CHL	SXT
Argentina	921	22	14	0	9	0.2	4	28
Brazil	865	30	8	0	5	0	1.5	48
Chile	737	26	7	0	17	0	2	29
Mexico	134	0	64	0	22	0	-	5
Paraguay **	88	32	17	0	6	0	2	49
Peru	32	50	34	0	6	0	12	56

* 1µg disk, <19mm. **≤5 years

PAHO continued from page 7

Costs of hospital infections

Studies from 14 hospitals in nine countries follow a common protocol promoted and published by PAHO.[14] These studies showed that hospital infections are prohibitively costly. For example, in Guatemala, the excess cost of treating a ventilator-associated pneumonia in adults is US $1,500 per case, and for neonatal pneumonia, $1,200. Considering that a hospital can annually treat 60 cases of ventilator-associated pneumonia in adults, this hospital infection alone will cost US $90,000 per year. Ventilator-associated pneumonia and urinary infections in adults in Paraguay cost an excess of US $8,700 and US $3,600 per case, respectively. Ventilator-associated pneumonia and catheter-associated blood stream infections in adults in Argentina cost an excess of US $4,800 and $2,600 per case, respectively.[14]

Clinical guidelines and formulary

In order to provide the countries with a practical intervention that can be implemented quickly to improve the rational use of antibiotics, PAHO developed and promoted the use of a model clinical guideline and formulary adapted to the Region. This model may also be adapted to the needs of each country. The guideline focuses attention on AMR throughout the health services, by improving patient care and promoting antimicrobial resistance surveillance in hospitals. Adapting this model in each country will require the collaboration of professors of infectious diseases, internal medicine, surgery, and other specialties, given that these academics are the real opinion makers on this issue. These same professionals will go on to teach better practices regarding the use of antibiotics to future generations of health care personnel in local universities. The 2004-2005 version of the guidelines is in use in most countries.[15]

Table 2. Species under surveillance and number of isolates tested (2003)

Hospital isolates		Community isolates	
Species	Number of isolates tested	Species	Number of isolates tested
Enterococcus spp.	5,800	*Salmonella* spp.	4,800
Klebsiella pneumoniae	12400	*Shigella* spp.	5,600
Acinetobacter spp.	8,700	*Staphylococcus aureus*	2,800
Pseudomonas aeruginosa	14,000	*Escherichia coli*	30,000
Staphylococcus aureus	22,000	*Campylobacter* spp.	1,700
Escherichia coli	23,000	*Streptococcus pneumoniae*	2,437
Enterobacter cloacae	4,800	*Haemophilus influenzae*	887

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HYGIENE continued from page 1

families. The most common sources of information and guidelines — those produced for health-care institutions and commercial food production — must be carefully adapted to consumers who are preparing foods, or caring for babies, children, the sick, elderly or disabled.

APUA and Clorox recognize this growing need for science-based recommendations to consumers. The 32-month cooperative project (September 2005–April 2008) will convene a distinguished group of experts in a series of scientific advisory board meetings, exploring the question: "What is responsible hygiene?" The panelists' recommendations will be synthesized in educational guidelines for use in homes, schools, daycare centers, and community worksites.

Participants and consultants will include U.S.-based and international experts in the fields of hygiene, disinfection, infectious disease, antimicrobial resistance, and health statistics, as well as representatives of medical societies and public health agencies. Participants will review and discuss the most recent findings on such topics as the hygiene hypothesis; biocide use and its relationship to antibiotic resistance; "targeted" hygiene; selection of appropriate disinfection products; and measures for cost-effective hygiene. Drawing on these discussions, participants will outline a scientific research agenda. The consensus of the group will be distilled into simple guidelines directed to lay audiences, and include a plan for dissemination. A national symposium will be convened at a major scientific professional meeting, with resulting recommendations submitted for peer-reviewed publication. The project's recommendations will eventually be tailored to a variety of international audiences.

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APUA NEWS

GAARD

As we begin the new year, APUA would like to acknowledge its partners for their vital contributions in preserving the power of antibiotics. This support sustains such programs as the Global Advisory on Antibiotic Resistance Data (GAARD) project, which was founded in 1998. GAARD is a global public-private partnership involving the world's largest independent surveillance systems tracking antimicrobial resistance (AMR). By coordinating data collection and joint analyses, the GAARD program identifies emerging drug resistance trends among the major infectious diseases in order to inform global public health policy and practice. GAARD's accomplishments over the past year include: the official release of the 2005 GAARD Report in *Clinical Infectious Diseases* in August; publication of a related GAARD study in the CDC's *Emerging Infectious Diseases* in June; the APUA Congressional Staff Briefing in July; and recognition in the *Wall Street Journal, USA Today,* and *Infectious Disease News.*

The GAARD Steering Committee meeting took place on December 17 at the 45th annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Washington, D.C., with plans for exciting new research initiatives. Topics under consideration for the coming year include community-

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**2004-Nov. 2006

APUA's research and educational projects are made possible through the generous support of private donations, government grants and individual memberships, as well as unrestricted grants from corporate contributors. APUA programs promote the prudent use of existing antimicrobials, as well as development of innovative products, diagnostics, antimicrobials, and vaccines. We are grateful to all of our corporate and project partners listed and welcome other collaborations to control antibiotic resistance and improve antibiotic treatment in the industrial and developing world.

Anibal Sosa, APUA International Program Director, with Anne Bolmström, President and CEO of AB Biodisk, who received special recognition at APUA's annual Members' Reception

associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) and *Acinetobacter*. Representatives of Glaxo-Smith Kline (The Alexander Network), JMI Laboratories (SENTRY), and WHONET attended this meeting, as did our new collaborators from AB Biodisk, Istituto Superiore di Sanità: Department of Drug Research and Evaluation (Italy), Laboratory Specialists, Inc., and the WHO Collaborating Centre for STD and HIV.

Other GAARD principals include: AstraZeneca Pharmaceuticals (MYSTIC), Bayer Healthcare, Brigham and Women's Hospital, Emory University, Ortho-McNeil Pharmaceuticals, Schering-Plough Corporation, U.S. Centers for Disease Control and Prevention, University of Alberta Hospital, University of Toronto-Mt. Sinai Hospital, and WHO Stop TB Department. We are grateful for these partnerships and look forward to another exciting year.

See www.apua.org for our 2005 GAARD Report and the full partnership list.

Attendees at APUA's annual Member Reception (from left to right): Patricia Cook (CDC), Todd Weber (CDC), Kate Gillepsie (APUA), Leadership Award recipient Richard Besser (CDC), and Silvio Vega (APUA-Panama)

Please contact Katherine Gillespie of the GAARD staff for more information on becoming involved in GAARD. Katherine.Gillespie@tufts.edu.

Member Reception and Corporate Sponsors

APUA held its annual Member Reception and Leadership Award Presentation at the 45th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington, D.C. on December 17. Dr. Richard Besser of U.S. Centers for Disease Control & Prevention received the APUA Leadership Award, in recognition of his national leadership in the *Get Smart: Know When Antibiotics Work* campaign. Anne Bolmström, President and CEO of AB Biodisk, was also recognized for her instrumental role in advancing the use of antimicrobial resistance testing by APUA Chapters. APUA would like to thank all of you who joined us for this eventful evening. We would also like to acknowledge our corporate sponsors and project partners for their generous support and invaluable collaboration in "Preserving the Power of Antibiotics®," including Wyeth-Ayerst Research for its support of this year's reception.

Consultant Opportunities for Antibiotic Resistance Projects

In addition to offering opportunities to collaborate with ROAR, GAARD, and international chapters, APUA welcomes your involvement in several new research and educational projects:

- Responsible Hygiene for a Healthy Household (exploring the relationships between household cleaning products, antibiotic resistance and the hygiene hypothesis)
- Antibiotic Resistance and Treatment Compliance
- Measuring the Economic Burden of Antibiotic Resistance

Please contact APUA at APUA@tufts.edu if you have specialized expertise and are interested in being considered for advisory board membership or consultancies on any of these projects. More detailed information will be posted soon on the APUA website at www.apua.org.

ROAR Accepting New Data

The Reservoirs of Antibiotic Resistance (ROAR) project, funded by the National Institute of Allergy and Infectious Diseases and coordinated by APUA, is an unprecedented effort to improve scientific understanding of the role of commensal bacteria in the spread of antibiotic resistance.

The ROAR Isolate Database, the cornerstone of ROAR's online interactive bioinformatics resource (see http://db.roarproject.org/ROAR/account/databases.htm), is currently accepting commensal isolate data. Interested investigators should contact ROAR staff (see below) for submission guidelines. Applicants who responded to the 2005 Request for Proposals will be notified in early March. For more information or to join the ROAR Scientific Network listserv please see www.ROARProject.org or contact Amelie Peryea (amelie.peryea@tufts.edu). Look for the new ROAR website in March.

In Memoriam

APUA lost a long-time supporter and friend in the passing of Dr. John F. Barrett in late January 2006. An accomplished infectious diseases microbiologist, John was Senior Director of Antimicrobial Drug Discovery at Merck and Company in Rahway, New Jersey. His career path had also taken him to other pharmaceutical companies, including Pfizer, Ortho-McNeil and Bristol-Myers Squibb. His contributions to the fields of microbiology and antibiotic resistance are internationally recognized. He was an unwavering advocate for appropriate antibiotic use and for the need to find new classes of antibiotics. Countless colleagues regarded him as a personal friend, and he will be sorely missed by APUA. We send our condolences to his wife, children, parents and siblings.

APUA INTERNATIONAL

AMR Workshop

A workshop on AMR Basic Research Methodologies was conducted in Lusaka, Zambia in October 2005. Seventeen health care professionals participated in the session, which was funded by the United States Agency for International Development (USAID)/MSH RPM Plus. The session was led by Professor Iruka Okeke, Ph.D., a member of the APUA Scientific Advisory Board, and APUA staff scientist John Stelling, M.D., MPH.

Health care professionals attending the training workshop on AMR research methodologies in Lusaka, Zambia. The course was led by instructors Iruke Okeke (back row, left) and John Stelling (back row, center).

South American Infectious Disease Initiative (SAIDI)

The USAID's Regional Bureau for Latin America and the Caribbean (LAC) has organized the South American Infectious Disease Initiative (SAIDI) to develop sound strategies to contain the spread of AMR in Bolivia, Paraguay and Peru. The SAIDI model promotes collaboration between technical organizations and governments, as well as information-sharing within South America. SAIDI will be jointly managed by the USAID/Peru Mission and the USAID Washington-based Regional Bureau for LAC. Partners in this venture are APUA, CDC, LinksMedia, MSH/RPM Plus, and PAHO.

PAHO-TAG

Dr. Anibal Sosa, APUA International Program Director, attended a PAHO-TAG (technical advisory group) meeting in Asuncion, Paraguay in December, 2005. At this biannual meeting, experts discussed issues related to AMR in PAHO's 16-nation AMR surveillance effort, and issued two-year recommendations. Additional information may be obtained by contacting Dr. Sosa at anibal.sosa@tufts.edu.

REACT

A seminar entitled "Will we respond to antibiotic resistance in time?" was held by the Action on Antibiotic Resistance (REACT) coalition in September, 2005 at the Karolinska Institute. Dr. Anibal Sosa attended, with other participants representing international agencies, the research community, industry, NGOs, consumers, civil society networks, media, and national civil service. For more information please visit: http://www.dhf.uu.se/react/.

APUA-Croatia

The 5th Croatian Symposium on Antibiotic Resistance will be held in Zagreb on March 17-18, 2006 in association with the International Society of Chemotherapy and APUA-Croatia. For more information please contact Arjana Andrasevic, APUA coordinator at arjana.andrasevic@zg.htnet.hr.

APUA-UK

Dr. Cliodna McNulty, Head, HPA Primary Care Unit at the Microbiology Department in Gloucestershire Royal Hospital, has assumed leadership of APUA-UK, replacing Peter Davey, M.D., who has become vice president of the British Society for Antimicrobial Chemotherapy (BSAC), the umbrella organization of APUA-UK.

Chapters in Development

The Council of the Federation of Infectious Diseases Societies of Southern Africa has unanimously supported the creation of the APUA-South Africa chapter, under the leadership of Professor Sabiha Essack, Dean of the Faculty of Health Sciences, University of KwaZulu-Natal, Durban, South Africa. Chapter development is also in progress in Ethiopia, Gambia, Ghana, Namibia, and Tanzania.

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Guidelines will be distributed to research scientists, healthcare providers, and policy makers. Recommendations will also reach the public and selected target audiences via the APUA website, selected listservs, and educational materials distributed at professional meetings. In addition, APUA will issue a special edition of its Newsletter, devoted to sanitation and infection control issues in the home.

The Responsible Hygiene project was launched in January 2006, with a Study Design meeting attended by APUA staff members and President Stuart Levy, M.D.; Donald Goldmann, M.D. of Harvard's Schools of Medicine and of Public Health; Stephen Brecher, Ph.D., Director of the Microbiology Laboratories of the Boston Veterans Administration Healthcare System; and Elizabeth Scott, Ph.D., Co-Director of the Center for Hygiene and Health in Home and Community at Simmons College.

Readers who are interested or who have special expertise in any of the above-mentioned topics, and who would like to be considered as a consultants or participating members of APUA's hygiene initiative, should contact Stephanie.Boyd@tufts.edu for additional information.

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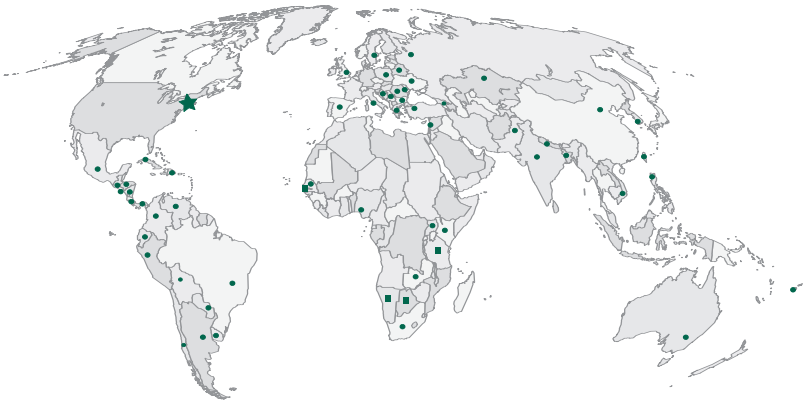

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