Antimicrobial Resistance in (AMR) Africa: Smoldering in the Shadows
by Madeline Drexler, Associate Editor

In the shadow of AIDS and other devastating epidemics, a more insidious health threat is spreading through Africa: antimicrobial resistance. Four of the top six infectious killers on the continent – acute respiratory infections, diarrheal disease, malaria, and tuberculosis – have increasingly defied first-line treatment. In this poverty-stricken continent, where per capita health allotments are meager, the greatest danger may be the impending loss of broad-spectrum, low-cost antimicrobials such as tetracycline, ampicillin, chloramphenicol, and the fluoroquinolones.

How serious and entrenched is antimicrobial resistance in Africa? Though the true magnitude of resistance is unknown, it is almost certainly underestimated, because reliable health data are scarce. Most African nations lack high-quality laboratories, surveillance networks, trained health workers, and other resources.

Social and Economic Conditions Spawn Resistance

Yet even if the precise boundaries of the problem have not been drawn, the consequences are well-documented. More Africans are dying of drug-resistant infections, especially in large outbreaks spawned by unsanitary conditions. Abundant reservoirs of resistance genes, such as E. coli (both in its commensal and pathogenic form), are transferring resistance to other disease-causing bacteria. And many resistant organisms spawned in Africa are poised to jump to other parts of the world – just as drug-resistant pathogens selected for in the developed world, such as ciprofloxacin-resistant enteric bacteria, may soon arrive in Africa, where they would swiftly spread.

“The worst-case scenarios are cholera and dysentery outbreaks, which can kill within a day, as well as the childhood diseases. These are infections where you don’t have a second chance to treat, cases that could lead to an enormous death toll,” says Iruka N. Okeke, Ph.D., M.S., APUA advisor for chapter development in Africa. “Milder infections – diarrhea in adults, some of the upper respiratory tract infections in adults, skin diseases – will be equally impacted. But those will bring a loss in productivity and an increase in the cost of treatment.”

In Africa, an array of deep-rooted social and economic problems has propelled the spread of antimicrobial resistance. Most African nations have at least one city growing at explosive rates, outpacing proper sewage disposal, water treatment, and other public health necessities. These crowded havens of urban migrants are breeding grounds for resistance, fueling the exchange of drug-resistant organisms between people and the transfer of resistance genes among bacteria. Crucial antibiotics are often in short supply, and the cost of medical care – even subsidized treatment – is out of reach for many patients. In many facilities, hospital infection control is rudimentary. And well-trained health workers have dwindled in number, especially in rural areas.

Life or Death Journeys

The very fabric of life in Africa also makes rational antibiotic use elusive. Some experts contend that antibiotics are too freely prescribed for acute infant diarrhea and childhood viral respiratory infections. But when patients travel long distances for treatment and are unlikely to return for follow-up visits, the alternative...
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can be even more harrowing. “For an individual in Africa, in many cases it’s a life-or-death situation,” says Okeke. “If a mother has to take her child with diarrhea on a three-hour journey to the hospital, she is not likely to come back the next day. Sometimes, her prescriber wants to know the mother has everything to insure that the child will get well. Very often, children and even adults with diarrhea or malaria will receive an antibiotic ‘just in case.’ And they end up taking it.”

AIDS and malaria further drive antimicrobial resistance. “People who are HIV positive take antibiotics almost continuously, creating selection pressure,” explains Okeke. “Until recently, malaria was treated with chloroquine – a drug that is active against parasites but has no activity against bacteria. Now that we’re seeing resistance to chloroquine, people are using alternatives such as sulfonamides and tetracyclines, which themselves can select for bacterial resistance.”

**Lack of Prescription Controls**

In Africa, the custom of casually self-prescribing antibiotics further raises the risk of resistance. Ready access to these drugs is a fact of life. One study showed that in pharmacy shops in southwestern Nigeria, 31 percent of the drugs sold were to self-prescribers. “That figure sounds strange to people in the U.S., but to anybody in Nigeria it sounds pretty normal,” says Okeke. “You learn to cook from your mother and you also learn what to do when you have diarrhea: buy tetracycline capsules.” In a separate study, Okeke found that university students entitled to free medical treatment – no less than isolated rural citizens – were treating their own infections.

Most self-prescribers do not buy or consume full courses of antibiotics – a practice that further selects for resistant bacterial strains. The southwest Nigeria study found that only 15 percent of customers bought full treatment regimens, in many cases because they could not afford it. “People buy their medication in bits,” Okeke says. “They will take it until they feel better, then stop and save what’s left for next time. Or they will keep buying a daily dose until they’re better, then stop.”

Unsanctioned providers often supply these self-administered drugs. In Africa as in many parts of the developing world, antibiotics are available on demand not only from hospitals and pharmacies, but also from patent medical salesmen, roadside hawkers, even such unlikely sources as purveyors of clothes, candy, cosmetics, and motorcycle parts. In rural areas, where the majority of Africans live, unsanctioned dealers dispense both oral and injectable antibiotics, and outnumber authorized providers. According to Okeke, the advantage of buying from unsanctioned providers is that their goods are cheaper, they are more accessible to residents of remote areas, and they are more likely to accept traditional beliefs about disease causation. On the other hand, these vendors are also more likely to dole out poor quality, expired, or illicitly obtained antibiotics, misdiagnose a patient’s condition, and mix batches and brands of drugs. Worst of all, they are usually oblivious to the long-term effects of antibiotic misuse.

**Quality Problems**

Whether purchased from sanctioned or unsanctioned providers, a large portion of antibiotics in Africa are below formulary

### Substandard Antimicrobial Medicines from Nigerian Pharmacies

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Below Pharmacopoeial Limits</th>
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<tbody>
<tr>
<td>Chloroquine phosphate</td>
<td>70-100%</td>
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<tr>
<td>Ampicillin</td>
<td>59-71%</td>
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<tr>
<td>Streptomycin</td>
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<tr>
<td>Isoniazid</td>
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<td>Metronidazole</td>
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Have you been hardened by tragedies like this? Are you less idealistic than you used to be?

A: I am a very keen admirer of what APUA has done in Latin America. They’ve managed to prove that you can do things in developing countries. Patients and prescribers are starting to learn that there is antibiotic resistance out there, that we should be careful about the drugs that we use. They’re starting to do surveillance studies there. What I’m hoping is that through our work, this APUA model will soon be replicated in Africa.

Dr. Okeke credits her interest and training in antibiotic resistance research to her thesis advisor and current collaborator, APUA Nigerian chapter coordinator Adebayo Lamikanra of Obafemi Awolowo University, Nigeria, and Dr. Robert Edelman of the University of Maryland Medical School.

Okeke was interviewed at her office on November 11, 2002 by APUA newsletter associate editor Madeline Drexler, author of Secret/Agents: The Menace of Emerging Infections.
Experimental Evolution of Antibiotic Resistance

Barry G. Hall, Biology Dept., University of Rochester, Rochester, NY, USA

Evolutionary biologists have a saying “Use it or lose it”, meaning that evolution tends to discard unused functions. The antibiotics equivalent might well be “Use it and lose it”! Our experience seems to indicate that the more an antibiotic is used, the more quickly its usefulness is lost as resistant strains appear.

We tend to view antibiotic resistance as an inevitable consequence of use, and to assume that resistance to all antibiotics arises with equal ease. That may not be the case. The spread of antibiotic resistance in microbial populations is the result of mutation, selection and migration of resistance genes among hosts, i.e. it is a purely evolutionary and population genetics problem. The current work in my lab is directed toward two aspects of the problem: predicting the evolution of known antibiotic resistance genes in response to selection by antibiotics, and determining where new, previously unknown, resistance genes come from.

Both approaches are experimental, rather than theoretical, and both are intended to provide practical approaches that can be applied by the pharmaceutical industry to the mutual benefit of that industry and to the healthcare community at large.

Predicting the Evolution of Known Antibiotic Resistance Genes

The identities and sequences of literally hundreds of antibiotic resistance genes are known. Like other enzymes, they fall into families based on the antibiotic substrates that they act on. For the purpose of this article I will consider the β-lactamases, although the arguments and approaches could be applied equally well to any other family we might consider. β-lactam antibiotics include the penicillins, cephalosporins, monobactams, carbapenems and their synthetic derivatives that have been developed as resistance to the natural antibiotics evolved. Most resistance to β-lactams comes from microorganism’s synthesizing β-lactamases, enzymes that degrade the drugs by cutting the β-lactam ring that all of the drugs have in common.

β-lactam antibiotics account for more than 50% of global antibiotic consumption because of their effectiveness and general lack of serious side effects. There are four families of β-lactamases, the TEM-SHV family, the OXA family, the AmpC family, and the metallo-β-lactamase family. The families differ not only with respect to sequence and structure, but also with respect to the range of β-lactam antibiotics that they typically hydrolyze effectively. At one extreme, TEM-1, the ancestor of the entire TEM family, hydrolyzes penicillins effectively, but hydrolyzes modern cephalosporins and carbapenems very poorly. At the other extreme, the metallo-β-lactamases hydrolyze all the β-lactamases well.

In vitro evolution dramatically speeds up the evolutionary process...at rates about 100,000 times higher than a living organism could survive.

Although TEM-1 hydrolyzes third and fourth generation cephalosporins, monobactams and carbapenems poorly, it has given rise to many descendants, the so-called TEM extended spectrum β-lactamases (ESBLs) that are quite active toward those more modern drugs. Indeed, within three to four years of introducing most β-lactam antibiotics into clinical use, members of the TEM family that confer resistance to those drugs have appeared. The major exceptions to that rule are cefepime, a 4th generation cephalosporin, and the carbapenems imipenem and meropenem. That rapid evolution in response to the use of new β-lactam antibiotics is largely responsible for our expectation that rapid evolution of resistance is an inevitable consequence of drug use. In the case of the TEM family, the rapid evolution is particularly distressing because the TEM β-lactamases are the most common of the plasmid-borne resistance determinants.

We would like to be able to predict whether any particular resistance gene has the potential to evolve the ability to confer resistance to a new drug. Cefepime is a relatively new drug, having been approved by the FDA only in 1996. So far no TEM enzymes capable of conferring clinical resistance to cefepime have been isolated. It might be the case that cefepime simply has not yet been used long enough and widely enough to have selected for cefepime-resistant TEMs, or it might be that the TEM enzymes do not have the potential to evolve to deal with that particular drug. My lab has been using experimental, or in vitro, evolution to distinguish those possibilities.

In vitro evolution dramatically speeds up the evolutionary process by introducing multiple random mutations into a target gene at rates about 100,000 times higher than a living organism could survive. The mutated genes are cloned and introduced into living cells, in this case E. coli, and the resulting population, called a library, is screened for increased resistance to the drug of interest. If increased resistance is detected, the improved mutants are subjected to one or more additional rounds of in vitro evolution until no further improvement is detected. Several methods of in vitro evolution have been developed, but we prefer a simple method that uses a highly error-prone DNA polymerase called Mutazyme™ (Stratagene) in a PCR reaction to introduce the mutations. One reason for that preference is that, unlike other methods, Mutazyme introduces a spectrum of mutations that is virtually identical to the natural mutations observed in E. coli.

How can we tell if in vitro evolution mimics nature sufficiently well that we can use it confidently to predict how genes will evolve in nature? We took advantage of the fact that nature has already evolved over 90 descendants of TEM-1 (see http://www.rochester.edu/College/BIO/labs/HallLab/index.html for phyllogenies of the TEM/SHV, ampC and OXA β-lactamases), the majority of which have the ESBL phenotype. We used our in vitro method to evolve the TEM-1 gene in nine separate lines, selecting for increased resistance to four different ESBL β-lactam antibiotics. We then sequenced our 10 in vitro evolved genes (two different genes from one of the lines) that conferred the ESBL phenotype and compared them with the naturally evolved ESBL TEM genes.
Experimental Evolution continued from page 4

The naturally evolved ESBL TEM genes include nine amino acid substitutions that have arisen independently on multiple occasions. Because those substitutions have occurred repeatedly they are likely to be responsible for the ESBL phenotype. If our in vitro evolution method accurately mimics nature it should generate primarily the same amino acid substitutions. Seven of the nine substitutions that occur repeatedly in natural ESBL TEM genes appeared in our ten in vitro evolved TEM genes, and six of those occurred repeatedly in our 10 evolved genes. We can conclude that our method accurately mimics natural evolution.

In the course of those experiments we obtained two mutants that conferred resistance to cefepime, something that has not yet been seen among natural TEM genes. We had not selected directly for cefepime resistance, instead cefepime resistance had been obtained indirectly while selecting in one case for aztreonam resistance and in another case for ceftazidime resistance. Because both mutants included a substitution of valine for isoleucine at position 173 we speculated that the I173V substitution might be important for cefepime resistance and that cefepime resistance might, indeed, evolve in natural TEM alleles.

Having demonstrated the validity of our method for predicting natural evolution we have now turned to asking whether natural TEM genes are likely to evolve cefepime resistance, and if they do so, what amino acid substitutions are most likely to be responsible for that resistance. Starting with TEM-1, we have now evolved eight different cefepime-resistant TEM genes. All eight have different amino acid substitutions, but the most common substitution is the I173V substitution. The most resistant gene has only three substitutions, while the second most resistant has six substitutions... remarkably those two genes have no substitutions in common. Clearly TEM-1 has found many different molecular solutions to the problem of hydrolyzing cefepime. Because we can demonstrate an order in which the mutations occur such that each improves resistance to cefepime, we can predict with great confidence that cefepime resistance will soon appear in nature. In the case of cefepime we would be well advised to use it as sparingly as possible.

The practical application of our method is that pharmaceutical companies can use the approach to evaluate how easily resistance to a new drug will arise when existing resistance genes are challenged by the clinical use of the drug. If resistance arises easily as the result of one or two mutations, then the probable useful lifetime of the drug may be fairly short. If, on the other hand, it proves to be quite difficult or impossible to evolve resistance, the drug is likely to have a long useful lifetime and we might be able to use it widely without worrying about resistance arising.

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Could we ever be confident that resistance would not arise? Yes, and we already have one such example. A particular gene in the chromosome of Salmonella is not expressed and does not confer drug resistance, but when that gene is mobilized to a plasmid and expressed it confers resistance to the aminoglycoside antibiotic tobramycin, and to a lesser extent to kanamycin. The resistance levels are not very high, however, so we used our in vitro method to evolve that gene for increased resistance to those drugs and for resistance other related drugs. After much effort we have been completely unable to improve that gene at all. In fact, we can be 97% confident that no single mutation or combination of double mutations improves the gene at all. In nature, mutations arise one at a time and each must measurably improve the gene if the mutation is to be successfully incorporated into the population. If no single or double mutation improves the gene we can be confident that there is no natural evolutionary pathway by which this particular gene can evolve to become a clinical problem.

The scale at which a small academic lab can work limits us to predicting the evolution of a single antibiotic resistance gene at a time, and limits us to considering less than ten independently evolving lines of that gene. Industry, on the other hand, can apply the method to new drugs on a much larger scale, for instance evolving representatives of all families of ß-lactamases simultaneously and evolving a hundred lines of each gene. There are many members of each ß-lactamase family, but phylogenetic analyses can be used to determine which genes should be selected for investigation. Why consider so many lines? Even our small scale studies have shown that there are many different mutations that can lead to the same resistance types. A large study is more likely to identify all of those solutions. With a large set of genes that confer resistance to a new drug, industry can begin developing the next generation of drug that will be able to withstand all of those genes that are likely to evolve. In effect, this approach gives industry not only the opportunity to assess how long a drug will remain effective in the face of evolution, but also the opportunity to have another drug waiting on the shelves when that resistance does evolve.

This work is a very practical application of evolutionary biology and it is hoped that, in the end, it will give us a much better understanding of what actually constitutes the prudent use of any particular antibiotic.

Bibliography
even culture media. “When I was in Nigeria,” says Okeke, “the cost of a single bottle of nutrient agar was more than a technician’s annual salary.” So dire are the shortages, that some lab workers have tried to fashion their own antibiotic disks from local blotting papers – a well-intended tactic that produces unreliable test results.

Such material deprivations have discouraged African scientists from embarking on basic research, the kind of studies desperately needed to map the true dimensions of antibiotic resistance.

With so many challenges, will Africa ever manage to turn the tide of antimicrobial resistance? Some observers believe it is possible – but only if the rest of the world mobilizes now, with funding and expertise. Among the most urgent interventions needed are: improved public sanitation and hygiene, more laboratories for culturing isolates and monitoring antibiotic quality, upgraded infection control, training for health workers both in the cities and countryside, education for both consumers and drug providers (including the unsanctioned providers who interact daily with so many Africans), and strong prescription guidelines.

With support from APUA International, applying the APUA chapter model to African Centers will allow for the successful coordination of such interventions. Africa may not soon reach the goal of completely rational antibiotic use. But in a place where simple, targeted measures have often led to far-reaching public health advances, every incremental gain will save thousands of lives.

For more information, contact anibal.sosa@tufts.edu.

EU Council Prohibits Antimicrobial Growth Promotants

The Agriculture Council of the European Union (EU) on December 16, 2002 approved new rules to prohibit the use of antimicrobial growth promoters in animal feed. The new EU Regulation will strengthen the control of all types of additives in animal feed, but in particular it completes the EU’s drive to phase out antibiotics as growth promoters. The EU has already banned antibiotics used in human medicine from being added to animal feed. The new Regulation will complete this ban on antibiotic growth promoters in feed by prohibiting the use of monensin, salinomycin sodium, avilamycin, and flavophospholipol. The final text of the Regulation is likely to be agreed upon during the first half of 2003, and the complete ban will take effect in 2006.

New APUA Scientific Advisor

APUA welcomes new APUA Scientific Advisory Board member, Iruka N. Okeke, Ph.D., M.S., Assistant Professor of Biology at Haverford College, and APUA chapter advisor for sub-Saharan Africa.

ROAR II Commensal Study

APUA’s Reservoir of Antibiotic Resistance Data (ROAR) II project, funded by NIAID, will facilitate the analysis of the relationship between resistance gene frequencies in commensal and pathogenic organisms, and develop tools for predicting the emergence of antibiotic resistance problems. The five-year study will advance knowledge concerning the “flow” of resistance genes among commensal and pathogenic bacteria. ROAR II represents the first organized effort to assemble and make available information on the genotypes and phenotypes of commensal bacteria that harbor resistance genes. The ROAR II Steering Committee is holding its inaugural meeting in early 2003. See the ROAR section of www.apua.org.
APUA Leadership Award
Presented to U.S.
Interagency Co-Chairs

(From left to right) APUA President Stuart B. Levy, M.D., Carole R. Andres, M.S. (accepting for Murray Lumpkin, M.D., of FDA) Marissa Miller, D.V.M., M.P.H. of NIAID, David Bell, M.D. of CDC, and APUA Executive Director Kathleen T. Young.

APUA members, partners and friends celebrated the year’s achievements at APUA’s annual member reception during the 42nd Annual ICAAC convention.

Stuart Levy, M.D., APUA President, presented the 2002 Leadership Award to the three co-chairs of the U.S. Interagency Task Force on Antimicrobial Resistance. David Bell, M.D., of the Centers for Disease Control and Prevention, Murray Lumpkin, M.D., of the Food and Drug Administration, and Marissa Miller, D.V.M., M.P.H., of the National Institute of Allergy and Infectious Disease were honored for their “extraordinary leadership and collaboration to preserve the power of antibiotics.” APUA is grateful for the generous support of this reception by Bayer AG, LIBRA, an international initiative to foster the appropriate use of antibiotics.

Bayer AG Joins GAARD

APUA’s Global Advisory on Antibiotic Resistance Data (GAARD), a public-private collaborative comprised of some of the world’s largest antibiotic surveillance systems, is pleased to welcome Bayer AG as a full member of the network. Bayer joins AstraZeneca Pharmaceuticals’ MYSTIC program, Bristol-Myers Squibb’s SENTRY program, and GlaxoSmithKline’s Alexander Network.

The GAARD Steering Committee met at ICAAC to discuss analysis of recently collected GAARD data, and to consider new research study possibilities. Included among the new data discussed were E. coli, Streptococcus pneumoniae and H. influenzae, which GAARD continues to track to supplement its 2001 study of H. influenzae.

APUA Testimony on FDA Position

As part of APUA’s ongoing effort to provide the latest scientific findings to inform public policy, APUA provided comments on the document “Guidance #152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern” to the FDA’s Center for Veterinary Medicine (CVM). Based upon the APUA “FAAIR Report” (published in June in Clinical Infectious Diseases), APUA recommended further incorporation of ecological considerations; cautioned about the underestimation of risk exposure assessment; suggested inclusion of qualitative approaches and the “precautionary principle;” and addressed the need for expeditious re-evaluation of existing approvals. See FAAIR at the ecology section of www.apua.org.

International Chapter News

APUA welcomes seven new chapters, increasing APUA’s global network to a total of 39.

New Chapters

Costa Rica: Led by Carla Odio Perez, M.D. of the Infectious Disease Department of the Children Hospital in San José, Costa Rica;

Croatia: Led by Arjana Tambic Andrasevic, M.D., Ph.D., of the University Hospital for Infectious Diseases, Zagreb, Croatia;

Nigeria: Led by Adebayo Lamikanra, Ph.D., of the Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria;

Pakistan: Led by Ghayor Khan, M.D., Ph.D., of the Hamdard University Medical Center, Karachi, Pakistan;

Panamá: Led by Sylvio Vega, M.D. of the University of Panamá, Panamá City, Panamá;

South Korea: Led by Ji So Ryu, M.D. and Yang-Soo Kim, M.D. of the Asan Medical Center, Seoul, South Korea;

Yugoslavia: Led by Sinisa Sevic, M.D. of the Clinic for Infectious Diseases in Serbia, Yugoslavia.

Field Training on AMR

Taiwan: Please note that Po-Ren Hsueh, M.D. is Taiwan Chapter Coordinator. This chapter has developed and distributed patient educational materials on antibiotic resistance in Taiwanese.

Argentina: Liliana Clara, M.D. worked with the Infection Control Committee of the Hospital Italiano in Buenos Aires to prepare educational materials for patients and clinicians.

Brazil: This summer, Helio Sader, M.D., Lauro Santos Ph.D., and Dr. Antonia Machado trained over 100 healthcare workers in the practice of antimicrobial resistance testing, with support from APUA’s Small Grants Research Program.

Ecuador: In collaboration with the Sociedad de Infectología del Ecuador, the chapter developed a guide for surgical prophylaxis and a training program for nurses on infection control committees. In collaboration with the Sociedad de Microbiología del Ecuador, Ecuador has also launched an Antimicrobial Resistance Awareness network to identify local patterns of antimicrobial resistance.

Chapters From Three Continents Share Lessons Learned

Effective local AMR programs was the topic of discussion at the APUA International Chapter Meeting on September 27, 2002, at the 42nd ICAAC conference. APUA Executive Director Kathy Young and APUA International Coordinator Dr. Anibal Sosa convened the meeting which included presentations by Dr. Celia Carlos (Philippines); Dr. Giuseppe Cornaglia (Italy); Dr. Waleria Hryniewicz (Poland); Dr. Peter Davey (United Kingdom); Dr. Jorge Panameño (El Salvador); Dr. Helio Sader (Brazil); Dr. Manuel Guzman-Blanco (Venezuela); Dr. Sylvio Vega (Panama); and Dr. Sheyla Silva (Nicaragua).
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Founded in 1981 as a nonprofit organization, APUA is the only organization in the world solely dedicated to strengthening society’s defenses against infectious diseases through research and education on antibiotic use and antibiotic resistance. APUA’s mission is to improve infectious disease treatment and control worldwide through promoting appropriate antibiotic access and use and reducing antibiotic resistance. With members in over 100 countries and numerous foreign affiliated chapters, APUA provides a unique network to support country-based activities and facilitate international planning and communication. APUA’s resources include an international scientific advisory board with members of national academies of medicine and science and a professional staff with specialized expertise. APUA’s global network of affiliated chapters serves to tailor interventions to local customs and practices.