# Report from the Field

## Escalating AMR in Acute Respiratory Pathogens

**Nguyen Thi Vinh**

APUA-Vietnam and Associate Professor, Vo Thi Chi Mai and Doan Mai Phuong, Hanoi Medical University, Dept. of Microbiology, Vietnam

Antibiotic resistance surveillance of common pathogens has been conducted since the 1990’s at 10 sentinel hospitals nationwide in Vietnam. This report presents an analysis of data collected from January 2004 to June 2006 in the two largest central hospitals: Bach Mai in Hanoi and Cho Ray in HoChiMinh City.

Of all specimen types (sputum, pus, urine, blood and other body fluids), sputa are the most commonly analyzed specimens. In addition, Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter species are the most commonly isolated bacteria from sputa.

## Global Experts Provide Perspectives and Clinical Advice

### Interview with Keith Klugman, M.B., B.Ch., Ph.D., FRCPath, Professor of Global Health, Rollins School of Public Health, and Professor of Medicine, Division of Infectious Diseases, School of Medicine at Emory University, Atlanta, GA, USA.

**Q:** What do you consider to be the greatest issue surrounding ARI in the least developed nations?

**A:** Development issues come first, which are now part of the global agenda. There are so many aspects to this. One would have to argue that most infectious diseases that kill, including respiratory infections, are greatly reduced if there is access to clean water. Over and above these fundamental development gaps, the single biggest issue is definitely access to point of care — meaning a doctor or nurse trained to prescribe antibiotics. It has to do with the whole infrastructure of healthcare in least developed nations. Timing is of the essence, because infected children die of exhaustion due to rapid breathing, which quickly overwhelms a body weakened through malnutrition. The Integrated Management of Childhood Illnesses (IMCI) program directly seeks to shorten the patient’s path to point-of-care, and to antibiotics.

Steve Black at Johns Hopkins and Shamim Qazi at WHO are among the leading experts in this area. The Integrated Management of Childhood Illnesses (IMCI) program directly seeks to shorten the patient’s path to point-of-care, and to antibiotics.

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European Research Progress Recognized at APUA Silver Anniversary Celebration

APUA held its Annual Members’ Reception at the 46th Annual International Conference on Antimicrobial Agents and Chemotherapy in San Francisco on September 28, 2006. More than 100 members and collaborators joined APUA staff members in recognition of APUA’s 25 years as a global-based non-profit organization dedicated to preserving antibiotic efficacy. Continuing in the tradition of honoring notable contributions in the area of antimicrobial resistance, APUA President, Dr. Stuart Levy, and Executive Director, Kathleen Young presented the 2006 APUA Leadership Award, which recognized the European Commission’s commitment to antimicrobial resistance research. Dr. Anna Lönnroth, of the European Commission Research Program, received the award for her outstanding leadership in mobilizing the European Commission’s research activities on antimicrobial resistance. Dr. Herman Goossens, of the Laboratory of Medical Microbiology at the University of Antwerp, received the award for his exemplary multifaceted research supported by the European Commission to promote the prudent use of antibiotics in humans.

Obituary

APUA Remembers Francis Tally

APUA lost a long-time supporter in the passing of Frank Tally, senior vice-president and chief scientific officer of Cubist Pharmaceuticals. Frank was a colleague of many of us working in infectious diseases at Tufts University School of Medicine, Boston, where APUA had its beginnings. He supported both the organization and the mission of APUA through his activities at Lederle (now Wyeth) when he initiated efforts to rejuvenate the tetracyclines through medicinal chemistry. This activity led to the development of Tygacyl, which has recently entered the clinical market. In fact, Frank can be credited not only with that new antibiotic, but also with developing Zosyn for Wyeth and more recently, Cubicin, for Cubist. Frank leaves a legacy of friends as well as outstanding accomplishments. We shall long remember his optimism, enthusiasm and tenaciousness, which rewarded him with the successes that he clearly earned. All of us at APUA will sorely miss him.
In general, resistance rates have climbed steadily in both hospitals and all five major pathogens are multi-drug resistant. Tracking of antibiotic resistance among *Klebsiella* isolates over a two-year period in both hospitals revealed sustained increases in resistance to all drugs tested (Fig. 2). Resistance in non-*Klebsiella* Enterobacteriaceae was similar to that in *Klebsiella*, and *P. aeruginosa* resistances (50% - 70% for CTZ and GEN) closely resembled those in *Acinetobacter* (Fig. 3).

In the first half of 2006, only 18% of *S. aureus* in Bach Mai were oxacillin-resistant, whereas it has escalated to 51% at Cho Ray Hospital. To date, no vancomycin-resistant strains have been recognized.

For *Klebsiella* and other non-*Klebsiella* Enterobacteriaceae, only three antibiotics (cefepime, imipenem and ertapenem) are still useful for treatment. Presently imipenem is the most active agent against these serious pathogens (Fig. 2, 3). However, treatment of *P. aeruginosa* and *Acinetobacter* remains problematic, especially in Bach Mai hospital.

What is the outlook and what can be done to treat infections caused by imipenem-resistant gram-negative bacilli? At present, the best recommendation is strict implementation of guidelines for the prevention of general nosocomial infection, with special emphasis on pneumonia. These interventions must be practiced universally across all hospital departments, with particular care in intensive care units. Concurrently, restriction of reserved antibiotics such as carbapenem and vancomycin must be strictly observed.

References
2. Ibid; 6: 16-22
3. Ibid; 7: 15-18
who may not be experienced in assessing pneumonia per se and may not give the appropriate antibiotic, or the appropriate dose. The World Health Organization (WHO) suggests that non-severe pneumonia can be judged by assessing fast breathing, whereas presence of lower chest indrawing or danger signs requires referral to a health facility with trained staff. (Table 1) Appropriate training and antibiotics need to reach all the involved caregivers, including local healers and community health workers.

Q: Could you comment on cotrimoxazole and current WHO recommendations in non-severe pneumonia?

A: Despite reported antimicrobial resistance, oral cotrimoxazole has been clinically effective for treatment of non-severe pneumonia. However, in high HIV settings, such as in Africa and elsewhere, it is now being used for prophylaxis to prevent pneumocystis infection in children with/or exposed to HIV, which will limit its clinical effectiveness. But it’s easy to give (two daily doses) and is less expensive — about a third of the cost of amoxicillin. WHO also recommends oral amoxicillin for non-severe pneumonia. Amoxicillin has likewise been shown to be effective in WHO-defined severe pneumonia.

Q: How might pharmaceutical companies assist ARI treatment in this setting? Would new classes of drugs be the best solution?

A: New classes would be a very useful addition. What we ideally need, however, is better diagnostics. C-reactive protein alone, or procalcitonin alone, is not enough to ascertain a bacterial infection. We can use them to triangulate alongside other blood tests. Chest x-rays are considered a “gold standard”, but if you show the same x-ray to 4 different specialists, you will probably get 2-3 different opinions. An accurate rapid diagnostic would be a really huge step forward for this field, because we know many children are dying due to the bacterial infections.

Q: Is the introduction of zinc and soap interventions promising?

A: While this makes sense, I think that such studies need to be replicated before being accepted as mainstream public health interventions. Hand washing is already an accepted intervention for diarrhea prevention, but for ARI there has only been one study to date. Zinc appears to reduce time spent in hospital for severe pneumonia in one study, but we are waiting for results from on-going research. At present while zinc is recommended by WHO for diarrhea management, it is not yet recommended for ARI management.

Q: Are there specialized pediatric doses for ARI?

A: It has been a practice for a long time to break pills and tablets for children in public health settings. Partly this is because some medicines are available in pediatric tablet formulations. Secondly, there are logistic and storage issues with liquid medicines. I don’t know of studies for pneumonia, but in one study in India the pharmacological availability from broken anti-TB tablet was reasonable. But if the active medicine is not evenly distributed in the tablet, potentially there might be a problem. I’m much more worried about whether the medicine is actually available at all when needed! WHO has started work on a pediatric essential drug list, led by Dr. Sue Hill. So when a list is prepared, after the consultative process is complete, potentially more essential drugs would be manufactured in pediatric doses.

Q: Are there any recent developments in ARI prevention/treatment?

A: A study in Guatemala introduced cooking stoves called “Plancha” that took smoke directly out of the house, which was compared with routine fuel in other houses (mostly open fire). Apart from reducing indoor air pollution, they found that this reduced pneumonia and respiratory infection rates in children. The study will be published shortly.

Measles, diphtheria, and pertussis vaccines are used practically in all countries, but coverage is sub-optimal in many places and needs to be improved. Haemophilus influenzae b vaccine has been used in all developed countries for some time now and is increasingly being used in developing countries with support from GAVI and public sector, but it still has some way to go. Although a 7-valent pneumococcal vaccine has been in use in developed countries for a few years, it is not yet being used as a public health measure in developing countries. The main reasons are the cost and the fact that commonly prevalent pneumococcal serotypes in the low resource settings are not all covered by this vaccine. International collaborative efforts are underway to develop
Acute Respiratory Infections in Mozambican Children: APUA Fact-finding

The southeastern African country of Mozambique is seriously affected by HIV, malaria and TB, and more than 50% of its population lacks access to standard health care. The rate of illiteracy is high (47% for females and 24% for males) and less than 10% of the population has a secondary or higher education. Life expectancy is 34 years.

In October 2006, APUA staff members Drs. Susan Foster, Aníbal Sosa, and Thomas O’Brien visited Maputo General Hospital and the Centro de Investigação em Saúde da Manhiça (Center for Health Research or CISM). The town of Manhiça is located about 90 km north of the capital, Maputo. Manhiça town and the surrounding villages have a population of about 36,600 inhabitants, with a density of 360 inhabitants/km². The people of Manhiça are mostly subsistence farmers and workers in an agricultural cooperative that grows bananas, rice and sugarcane.

The objective of the APUA mission was to discuss the findings of a recent study performed on acute respiratory infections in children. The CISM is a peripheral research centre of the Mozambican Ministry of Health and maintains strong ties to the Hospital Clinic of Barcelona. It is adjacent to an 80-bed health center, which includes a busy outpatient clinic, a maternity and child-care unit with an expanded immunization program and nutritional services, and an HIV clinic. The APUA team met with CISM staff members Drs. Pedro Alonso and Anna Roca and also visited the microbiology laboratory, the demographic surveillance center and other CISM facilities. The Centro and its staff have been noted recently for their work on the malaria vaccine, in which they found that vaccine efficacy for severe malaria was 57.7% and vaccine use reduced prevalence of P. falciparum infection by 37%.

Concurrent with its research on malaria, the CISM staff also investigated acute respiratory infections, which are the greatest cause of mortality in young children in the developing world. A strong association was found between malaria and severe lower respiratory tract infection.

Of particular interest to APUA is the extent of resistance to commonly used antibiotics in invasive pneumococcal isolates from young children. In a surveillance study of approximately 200 pneumococcal isolates from children 5 years or under, resistance to cotrimoxazole was the most prevalent at 10% (intermediate resistance = 27%), followed by intermediate resistance to penicillin at 14%.

APUA is interested in the dynamics of malaria, HIV and respiratory infections in the developing world, as well as the potential for implementing life-saving interventions, particularly in young children. It is currently gathering and assembling literature on practical, low-cost, region- or country-based methods that have proved useful in lowering morbidity and mortality and/or antibiotic resistance in rural areas. Such methods will be assessed for future publication and may be shared with APUA by contacting Susan Foster at: susan.foster@tufts.edu.

References
1. Alonso PL et. al., Lancet 2004; 364: 1411-20

Guided by Dr. Elizabeth Coelho, Chief of Laboratory Services APUA staff member, Susan Foster visits with microbiologists at the Maputo General Hospital

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Q: Besides antibiotics, are there any other interventions for ARI that you would like to see emphasized?
A: Recently there have been articles pointing out that access to soap makes a huge difference in pneumonia mortality, and to pneumonia and diarrheal figures generally.* I would also like to point out that there has been work by Zulfiqar Bhutta and others that indicates that an increase in zinc in the diet will reduce ARI infections.

Procalcitonin could be quite valuable in a western setting to reduce inappropriate use of antibiotics for bronchitis and other similar indications. In a least developed nation setting, I am less of an advocate than I was earlier. We did a head-to-head study with CRP (C reactive protein), which performed just as well, if not better than procalcitonin, and is certainly much much cheaper. In a Western setting, CRP has been somewhat discredited by factors that I really believe are just starting to be understood. Bacterial respiratory infections are almost always precipitated by a viral infection. When dealing with a proven viral infection, CRP gives off what we understand as a “false positive,” but we now have considerable evidence from vaccine studies that implicate a bacterial superinfection. Consequently, I think CRP has been underappreciated. The most important intervention is access to pneumococcal conjugate vaccine.

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APUA Suggested Reading
Please visit the APUA website at www.APUA.org for a list of current suggested reading.
Minimal Essential Sustainable Microbiology for the Developing World

Thomas F. O’Brien, M.D.
APUA Vice President and Medical Director of Microbiology, Brigham and Women’s Hospital, Boston, MA; Associate Professor of Medicine, Harvard Medical School, Boston, MA

Background
Infections have shortened human lives more than all other causes but were seen only as crude clinical syndromes until late in the nineteenth century. Microbiology then began to identify the microbes causing and specifying each of the infectious diseases. This enabled medicine to diagnose them in patients, measure their burdens on public health and take measures to prevent them by immunization and containment.

When antimicrobial agents were discovered a half a century later, they could, astonishingly, kill most pathogens and cure most severe infections. After wide use of each, however, pathogens developed resistance, treatments failed and treated patients remained sick or died. Microbiology laboratories began to test each patient’s pathogen to find an agent that could still kill it and cure that patient. While the testing was underway, the patient could be treated empirically with an agent that had tested effective recently for similar pathogens from local patients.

The microbiology gap
Antimicrobials then outran microbiology. Drugs went everywhere, but microbiology lagged. Medical centers in many parts of the world have rooms labeled “Microbiology” that prove to have very little function.

Microbiology often shares with chemistry or other clinical laboratories resource limitations that include training, quality-assurance, supplies and equipment, but it also has others of its own. New instruments may improve other resource-limited laboratories, for example, but often not the core work of microbiologists, whose special methods also tend to seclude them from oversight and accountability. Comparisons with wasteful practices in rich nations prompt despair.

Cost of the microbiology gap
A microbiology laboratory has a public health function that no other clinical laboratory has. What the others measure (serum sodium, hematocrit, etc.) is within and of use only to the person tested. Microbiology samples pathogens that move between people. Few patients in a resource-limited country may access and benefit from tests of the other laboratories, but microbiology can report from the few the pathogens and resistance genes that are coming to all of them.

Caregivers at medical centers that lack microbiology services treat infections blindly, not knowing the causative agents or what anti-infective could still be active. They are thus unable to learn from experience or advise caregivers in the vast areas with high infection rates and resistance, but few available agents, for which they may be the only distribution center.

The concept of “minimal essential sustainable microbiology” (MESM)
The concept is based on three observations. A small proportion of the total tests commonly done yield much of the information about serious community-acquired infection. Those tests require trained technicians, but are inexpensive. Epidemiological significance of accumulating results depends on systematic patient sampling.

The Mahiça example
The CISM laboratory in Manhiça, Mozambique (See Acute Respiratory Infections in Mozambican Children, p. 5) did blood cultures on all infants admitted to the adjacent district hospital and on older children (<5yr) admitted with a temperature >102°F. The identification and antimicrobial susceptibility of the pathogens isolated provided locally unprecedented data on the burdens of disease that each caused and the agents to best treat each disease. Culturing blood focused on invasive diseases. Making it mandatory systematized sampling.

Minimal essential microbiology 1: blood culturing
The Manhiça example shows that systematic use of one kind of culture (blood) can generate more useful information, probably for the infected patients and certainly for the surrounding communities, than the wider menu of kinds that resource-limited laboratories commonly attempt to offer and their caregivers use erratically or not at all. Mandatory culturing of blood from all febrile patients on admission before treatment is the first part of minimal essential microbiology.

Minimal essential microbiology 2: microscopy
A second requirement is microscopy. A microscope, glass slides and a set of stains support identification of blood cultures isolates and diagnosis and management of malaria, tuberculosis and parasites.

Minimal essential microbiology 3: special tests and data management
The first essential special test is HIV testing. Others may follow as technology develops. All results of all tests should be entered into, and reported from, a dedicated database and the databases linked into multi-center networks for real-time surveillance, analysis and continuous quality improvement. Software for this can be downloaded free from a WHO website: ftp://ftp.who.int/medicines

Sustainability
Needed equipment is a refrigerator, freezer, incubator, autoclave, sink, bench, alcohol lamp, inoculating loops, microscope and personal computer. Required supplies are bottles, tubes, petri dishes, dehydrated media, selected biochemicals, sheep blood, antimicrobial test disks, glass slides and stains. Costs are small and may be further reduced by coordinated purchasing for multiple laboratories.

Training is at the technical level, requiring basic biology and microbiology, initial mentoring, periodic updating and proficiency-testing, experience, ongoing internet-supported collegial consultation, problem-solving and continuous quality improvement. A laboratory might need two technicians.

Program
The initiative is seen as a program to define and publicize the need for minimal essential sustainable microbiology; survey the capacity of existing laboratories to provide it; advise and coordinate resources for those seeking to upgrade to or initiate it; provide instructional materials; and support development of computer networking for technical updating, collegial...
Household Hygiene Project

On September 19, the Hygiene for a Healthy Household project held its second advisory board meeting, which opened with a presentation by Dr. Syed Sattar on microbial chemical uses in domestic settings. The presentation spawned discussion on the need for an ecological approach to household hygiene as it is important that consumers be educated, not only on how and where to disinfect in the home, but also on how to use products safely and in manners that are relatively friendly to the environment. The group is working within this framework to develop a structure for the publication of project outcomes. APUA is also developing contacts with community groups that have an interest in using the project’s hygiene guidelines to educate the populations that they serve. The Hygiene Project is supported by an unrestricted educational grant from Clorox. For more information visit http://www.tufts.edu/med/apua/Research/hygiene.html or contact Stephanie Boyd at Stephanie.Boyd@tufts.edu.

APUA Fields Antibiotic Use Questionnaire in U.S.

During recent months APUA has worked with a multidisciplinary board of experts to develop a national survey that explores antibiotic use patterns of consumers across the United States. The survey was fielded by Links Media during the months of September and October, and preliminary results are beginning to come in. The data at this stage reveal some interesting trends and show potential usefulness for the development of new interventions to decrease patient misuse of antibiotics. Of particular importance are emerging data on the powerful effect of health care provider communication on patient behavior. APUA is currently working with project advisers to analyze the data and develop appropriate messages and recommendations for clinicians and consumers.

The Antibiotic Use Project is funded by an unrestricted educational grant from Pfizer. For more information on this project, visit http://www.tufts.edu/med/apua/Research/antibiotics_consumer.html or contact Stephanie Boyd at Stephanie.Boyd@tufts.edu.

APUA-Namibia

With sponsorship from the Izumi Foundation, APUA-Namibia held its first AMR Symposium in Windhoek, Namibia on September 20th, 2006. The session was conducted by Chapter President, Mrs. Dawn Pereko, (B. Pharm), Mrs. Joyce Namuhuja, Mr. Sherif Moustafa, Dr. Braum van Gruenen and Dr. Alec S. Bishi. APUA staff members Dr. Anibal Sosa and Michael Hricz attended.

APUA-India

APUA and the Voice of America (VOA) are joining forces to coordinate a training on antimicrobial resistance for health journalists. In preparation for the upcoming training session, Dr. Anibal Sosa, APUA Director of Global Chapter Network, met with APUA-India chapter coordinator, Prof. J.S. Bapna and reporters from the Rashtriya Sahara and Rajasthan Patrika newspapers in Jaipur. In New Delhi, he visited WHO South East Asia Regional Essential Drug and Medicines Policy Advisors, Drs. Krisantha Weerasuriya and Kongthong Thimasarn (Malaria), Ms. Laksmi Suebsaeng (AIDS), Dr. Nani Nair (TB), and Dr. Rajesh Bhatia (Blood Safety and Clinical Technology). He also consulted with Dr. Swarup Sarkars, Regional Program Advisor, UNAIDS Regional Support Team Asia and Pacific. ReAct media specialist consultant, Mr. Satya Sivaraman facilitated a meeting with Mr. Rajesh Kalra, Chief Editor, The Times of India Group, and Mr. Vipul Mudgal, Associate Editor, The Hindustan Times.

The training session is being planned for 2007. A related document designed for the public and health journalists can be found on the APUA website at www.tufts.edu/med/apua/tools/trainingguide.pdf.

APUA-Peru

APUA congratulates Dr. Cesar Sangay, who has been elected the new APUA-Perú chapter coordinator.

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analysis and interpretation of test results and detection of outbreaks. The program would develop and publicize standards and perhaps certify their attainment to call attention to the existing deficiencies and motivate for their correction.

Implementation

An APUA chapter in any country could work with the program to evaluate systematically the status of microbiology in that country, and advocate for and assist the country’s health officials in moving forward to establish MESM in one or more centers. The program could support the development, linkage and initial oversight, but not the eventual ongoing operation of such units.

The program is not meant to confine laboratories to minimal essential microbiology, but only to insure that some users exist. Any country fortunate to already have one or more well-functioning laboratories would be encouraged to include them in the network in a leadership role. Some of those may prove in practice to have deficiencies that the program could detect and ameliorate, but few are likely to have now the mandatory blood culturing of febrile patients on admission that assures uniform sampling.
If you are concerned about the public health threat of antibiotic resistance, become part of the solution. Make a tax-deductible contribution and join our global network of citizens, clinicians, researchers and policy makers.

Alliance for the Prudent Use of Antibiotics
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... containing global antibiotic resistance through local action

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 over 55 affiliated country chapters, APUA provides a unique network to support country-based activities and facilitate international planning and communication. APUA’s resources include an international scientific advisory board with members of national academies of medicine and science and a professional staff with specialized expertise. APUA’s global network of affiliated chapters serves to tailor interventions to local customs and practices.

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