Acute otitis media is the most common bacterial infection in infants and children. Thus, large amounts of antibiotics are prescribed for children with this disease, especially for those with recurrent episodes of acute otitis media. The peak incidence of acute otitis media is seen at the age of one to two years. The risk of developing another acute otitis media within one month after the onset of the primary infection is estimated at 35%. About 5% of children are “otitis-prone”, which is defined as six or more episodes of AOM during a one-year period or, alternately, as three or more episodes during a one-year period. The latter, more recent, definition results in a considerably higher detection rate.

Antibiotics with a Chaser of Bacteria?
Recolonization with commensal bacteria reduces recurrences of acute otitis media and pharyngotonsillitis

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Acute otitis media is the most common bacterial infection in infants and children. Thus, large amounts of antibiotics are prescribed for children with this disease, especially for those with recurrent episodes of acute otitis media. The peak incidence of acute otitis media is seen at the age of one to two years. The risk of developing another acute otitis media within one month after the onset of the primary infection is estimated at 35%. About 5% of children are “otitis-prone”, which is defined as six or more episodes of AOM during a one-year period or, alternately, as three or more episodes during a one-year period. The latter, more recent, definition results in a considerably higher detection rate.

The Future of the Quinolones
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The quinolone class of antimicrobials is now in its fifth decade. Quinolone use began modestly with the chance identification of nalidixic acid as a byproduct of chloroquine synthesis and its limited use for treatment of urinary tract infections. This was followed by stages of structural modifications that have expanded antimicrobial spectrum, improved pharmacokinetics, and both improved tolerability in some cases and explored its limits in others. Increasing use of quinolones for an ever broadening number of indications has established the class along with the later generation cephalosporins and the carbapenems as one of the three major broad-spectrum classes of antimicrobial agents. However, the quinolones, in contrast to the third- and fourth-generation cephalosporins and the carbapenems, are available in oral formulations with high bioavailability, adding further to their appeal. With increasing use of quinolones there has been, not surprisingly, the emergence of resistance to quinolones at clinically important levels among a number of bacterial species, and it is this emergence that represents the biggest threat to the future utility of the class.

Risks and determinants of the emergence of quinolone resistance

As synthetic agents, the early quinolones started their clinical careers without a
RECOLONIZATION continued from page 1

A considerably greater number of children who are regarded as otitis-prone.

The most common bacteria found in acute otitis media are *S. pneumoniae*, *H. influenzae* and, less often, *M. catarrhalis* and group A beta-streptococci. These bacteria originate and spread from the nasopharynx via the Eustachian tube to the middle ear cavity. Carlin et al. showed that 75% of the bacteria found in recurrent acute otitis media represent a different bacterial strain from the strain responsible for the original infection. The remaining 25% could be a reinfection with the same bacterial strain or a relapse (treatment failure).

Secretory otitis media is the most common sequela of acute otitis media. One or more of the bacteria mentioned above are found in about 30% of cases of secretory otitis media.3

**Normal flora**

The significance of the normal flora for protection against infection in an ecological niche has recently been stressed regarding the upper respiratory tract and lack of interfering bacteria, especially the alpha-streptococci, is associated with a high incidence of reinfections in streptococcal pharyngotonsillitis.4,5 Low numbers of alpha-streptococci have been found in the nasopharynx of otitis-prone children as compared to non-otitis-prone children,6 and in children with secretory otitis media as compared to healthy children.8 Alpha-streptococci isolated from the adenoid tissue have less growth-inhibiting capacity against isolates of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. pyogenes* (group A streptococci)9 were used in the spray. The spray was given into each nostril twice a day for ten days.

Out of 132 included and randomized children, 108 were eligible (53 in the alpha-spray group and 55 in the placebo group) for efficacy analysis. The mean age of the patients was 23 months.

The recurrence rate during the follow-up period of three months was significantly reduced in children given alpha-streptococci as compared with the

**Figure 1. Recurrence of acute otitis media**

All patients had a history of at least two earlier episodes of acute otitis media during the last six months or five episodes during the last year. At the next occurrence of acute otitis media the child was included in the study.

All children with acute otitis media were treated with antibiotics (amoxicillin-clavulanic acid or penicillin-penicillin) for ten days at inclusion followed by a spray of either alpha-streptococci or placebo. Alpha-hemolytic streptococci (two strains of *S. sanguis*, two *nitis* and one *oralis*) selected for their good growth-inhibiting capacity against isolates of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. pyogenes* (group A streptococci)9 were used in the spray. The spray was given into each nostril twice a day for ten days.

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The recurrence rate during the follow-up period of three months was significantly reduced in children given alpha-streptococci as compared with the
placebo group. In total, 42% of the children in the alpha-streptococcal group experienced no acute otitis media during the study and had a normal tympanic membrane at the last valid visit. In children given placebo, this figure was 22%.

**Figure 2. Rate of secretory otitis media**

![Rate of secretory otitis media](chart)

In children without recurrence, bacterial spray reduced the rate of secretory otitis media at last valid visit. *Significant at p=0.05.

(p=0.02) (Figure 1). Furthermore, in the group of children without recurrence who were given alpha-streptococci (n=32), ten (31%) had secretory otitis media at the last valid visit. In the corresponding placebo group (n=27), secretory otitis media was present in fifteen (56%) (p=0.05) (Figure 2).

**Recolonization**

Factors proven to be important in recurrent acute otitis media are heredity and an age of less than two years. Other factors often discussed in this regard are passive smoking, breast-feeding, number of siblings, and type of day care and allergy, but studies of these factors are not as conclusive. We would also like to add a disturbed normal flora as an important factor in recurrent acute otitis media.

The 50% recurrence rate within three months shown in this study in otitis-prone children after adequate antibiotic treatment emphasizes the need to actively help these children. This is further stressed by the high frequency of secretory otitis media. As many as 78% of the children treated with antibiotics and placebo either had a recurrence or still had secretory otitis media after 3 months. Antibiotic prophylaxis, either long-term seasonal treatment or intermittent treatment in relation to viral infection, are methods used to reduce the frequency of new episodes of acute otitis media in children with recurrent acute otitis media. However, these types of antibiotic treatment have been questioned in view of the growing antibiotic resistance of respiratory tract pathogens. Tympanostomy tube placement has been practiced and seems to effectively prevent recurrent acute otitis media in these children. However, the risk involved in this procedure as well as the cost of this operation, which must be performed under general anesthesia, in addition to complications and sequelae related to the tympanic membrane, have been pointed out.

Studies have shown that persons lacking interfering alpha-streptococci on their tonsils get more streptococcal throat infections than persons with alpha-streptococci present to inhibit the beta-hemolytic streptococci. Furthermore, Roos et al. have shown that patients with recurrent streptococcal pharyngotonsillitis get fewer recurrences after recolonization with a mixture of four alpha-streptococcal strains shown to have good growth-inhibiting activity against group A streptococci.

Treatment with interfering alpha-streptococci resulted in a significantly decreased number of recurrences of acute otitis media compared to children given placebo. In addition, it was found that this difference was also seen in children with secretory otitis media at the last valid visit.

The results of colonization studies, both in patients with streptococcal pharyngotonsillitis and in children with recurrent acute otitis media, are indicative of an important principle and emphasize the significance of a normal balance between microorganisms in the upper respiratory tract. In these studies alpha-streptococci were used, but it has recently been suggested that other bacteria such as *Prevotella* and *Peptostreptococcus* species show interfering activity in the upper respiratory tract and could therefore be candidates for ecological interventions. Most antibiotics used to treat infections in the upper respiratory tract have an impact on the normal bacterial flora, including the dominating alpha-streptococci. As these bacteria are part of the natural defense, treatment with antibiotics abates this part of the defense system and thus facilitates colonization with pathogenic bacteria. Repeated courses of antibiotics might thus paradoxically contribute to recurrent infections in otitis-prone children and in tonsillitis-prone patients. Restoration of the normal flora would therefore be the logical way to inhibit further recurrences of otitis media as well as streptococcal pharyngotonsillitis.

**REFERENCES**

large reservoir of preexisting resistance determinants in nature. But as was learned early on, spontaneous bacterial chromosomal mutations in the genes encoding the subunits of DNA gyrase, one of the two drug target enzymes, exist in small numbers in all large bacterial populations. Other similarly occurring chromosomal mutations alter topoisomerase IV, the second drug target enzyme, and also affect drug permeation to these two targets.

With the seeds of resistance present in all large bacterial populations, why then have the quinolones been successful overall for such an extended period and will the future be any different? Our answers to these questions are as yet incomplete, but recent efforts to model the dynamics of resistance emergence and analyses of risk factors in those pathogens in which quinolone resistance has been most extensive have provided some insights. In most studies in which factors associated with having a quinolone-resistant pathogen versus a quinolone-susceptible pathogen of the same species have been studied, use of quinolones is identified as a strong risk factor, even accounting for the overestimation of the effect of drug exposure in studies using this type of comparison. Thus, the clinical success of the quinolones in individual patients is at the same time a risk as larger populations of patients are treated.

Once quinolone resistance emerges to a substantial level, it is clear that spread of resistant infections from exogenous sources, such as between patients and between humans and animals, augments the selection pressures from quinolone use. In hospitals, nosocomial pathogens such as methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa have developed substantial levels of quinolone resistance over time, and in the case of MRSA, emerged relatively rapidly and to levels exceeding 90% of strains in many hospitals. For both S. aureus and P. aeruginosa single chromosomal mutations can cause clinically important levels of resistance, but nosocomial spread of resistant strains also makes a substantial contribution to the prevalence of resistance for both pathogens. For methicillin-resistant staphylococcal strains, which are usually multidrug-resistant, co-selection by exposure of patients to any of several antibiotics to which the organism is resistant (not just quinolone exposure) contributes to selection pressures. It is also intriguing to speculate that the ability of quinolone exposure of already resistant strains to increase the expression of fibronectin-binding proteins (which mediate staphylococcal adherence to body surfaces) may provide an additional mechanism by which quinolones promote the spread of quinolone-resistant strains.

Non-human reservoirs of resistant pathogens can affect the risk and prevalence of resistance in human populations. Travel to areas of high prevalence of quinolone resistance in the zoonotic pathogen Campylobacter jejuni have been shown to increase the risk of resistant campylobacter enteritis, which responds more slowly to quinolones than enteritis caused by a susceptible strain. Resistant campylobacters have been identified in food production animals, particularly poultry, and in food, and quinolone-resistant campylobacters from poultry sources increased following the approval of therapeutic use of quinolones in poultry production.

Particularly troublesome is the emergence of resistance in some originally highly quinolone-susceptible pathogens, such as Escherichia coli and Neisseria gonorrhoeae. For both of these pathogens, multiple mutations are required for clinically important levels of resistance to emerge, suggesting that resistance should be infrequent, and in some areas, such as the US, this is still the case. In other areas, however, there is a substantial prevalence of resistant strains. For E. coli, rates of resistance are particularly high in Europe and the Far East. In Spain, studies have identified resistant E. coli in food animals, and resistant strains were found colonizing the fecal flora of at least a quarter of outpatients, including children, who would not be expected to have had direct exposure to quinolones. Traditionally, E. coli with toxinogenic or other mechanisms of causing diarrheal disease were considered to be zoonotic and foodborne in origin, but contamination of food with commensal but resistant strains raises the possibility that a human reservoir of resistant E. coli may have arisen in some areas of the world, in part by seeding of resistant strains from food sources. Human use of quinolones acting on patients colonized with such resistant strains may in part explain the highly resistant E. coli bacteremias in neutropenic cancer patients given quinolone prophylaxis reported from Europe, but not the US.

The only known natural reservoir of N. gonorrhoeae is humans, and spread of strains occurs in the community. In the US, quinolone-resistant gonococcal infections have been infrequent overall and have generally occurred in outbreaks of spread of clonal strains in which quinolone use itself has not been a risk factor. Rates of resistance have been highest in the Far East, but the factors that cause such a high prevalence of resistance in these areas are unclear. Use of unlicensed quinolone formulations of low potency has been reported in this region, and it is speculated that such use may have produced both microbiologic failures and step-wise selection of multiple mutations in the persisting N. gonorrhoeae strains. Laboratory and animal studies show that long concentrations of active quinolone increase the frequency of selection of resistant mutants. Resistant gonococcal strains have also appeared outside the Far East and in some cases have been linked to travelers to the Far East. Thus, due to the current ease of global travel, a reservoir of resistant pathogens in one part of the world becomes a risk to other areas.

The future of quinolones depends on the future of resistance

Recently, new quinolones are being used to treat community respiratory infections, driven in part by rising resistance to other classes of antimicrobials, particularly in Streptococcus pneumoniae, for which multidrug-resistant strains may constitute up to a third of clinical isolates. New respiratory quinolones remain active for the most part against these strains, but reports of rising quinolone resistance, albeit...
still at low prevalence, are a cause for concern. The propensity of resistant *S. pneumoniae* strains to spread clonally also highlights this concern. Needed measures to protect the future utility of the quinolones include 1) controlling quinolone use to reduce selection pressures, 2) minimizing usage in reservoir populations (in the case of pneumococci, children, who more commonly harbor and spread *S. pneumoniae*), and 3) practicing good infection control activities to prevent spread of resistant strains in nursing homes, daycare centers, and hospitals, depending on the habitat of the pathogen.

The pharmaceutical industry has been successful heretofore in developing quinolone congeners with increasing potency against a broadening range of pathogens, and in some cases these increments in potency have been sufficient to overcome earlier levels of quinolone resistance. It is likely that there will remain a need for newer quinolones that are able to address emerging resistance. At what point a limit will be reached is difficult to predict, since this class has had over its five decades some surprising resurgences following apparent stagnation. Toxicities have plagued some of the most potent recent candidate drugs, so that balances of tolerability, spectrum, and potency will always come into play as new candidates are developed. The challenges for development are substantial, but congeners with novel structures and striking potency (e.g. 2-pyridones and desfluoroquinolones) provide hope for future drugs to deal with current resistances. A parallel approach is to prolong the lives of current quinolones by investigating appropriate combinations of quinolones with other antimicrobials, possibly to enhance efficacy, but particularly to reduce resistance. Limited data support the concept that combinations of quinolones with other antimicrobials may reduce resistance selection, but more data are needed.

Thus, the future of the quinolones depends on many factors, but many of the factors illustrated above are potentially modifiable at least in part, providing hope that, with efforts at good stewardship of these valuable agents, their lifespan can be prolonged.

References

Are antibiotics always needed immediately for acute otitis media? Is delayed prescribing a viable approach?

Otitis media is one of the most common acute respiratory conditions managed in primary care, yet treatment is controversial.1-3 Most children with otitis media who visit their doctor are prescribed antibiotics, but a systematic review suggests only marginal benefit from antibiotics; in the week after seeing the doctor, only one child benefited symptomatically for every 18 children treated.4 Considerable debate continues as to the nature and magnitude of benefit from antibiotics in patients with acute otitis media. Conflicting findings were reported from a large trial from a typical primary care setting.3 On the one hand, antibiotic use gave only a very small reduction in analgesic (paracetamol) consumption, which suggests that the perceived pain and distress may be little affected by antibiotics.

Immediate vs. delayed antibiotics

The efficacy of immediate vs. delayed antibiotics for acute otitis media was tested in a recent UK trial.7 Three hundred fifteen children presenting with acute otitis media to a primary care doctor were randomized to a) immediate antibiotics, or b) delayed antibiotics. The delayed antibiotics protocol involved the doctor advising parents to wait 72 hours from diagnosis before obtaining an antibiotic prescription on request. Parents were advised to collect the prescription if the child still had significant otalgia or fever by 72 hours, and/or was not starting to improve, or developed a discharge that lasted for more than 10 days. The doctor maximized the placebo effect in each group by a series of strongly supported structured statements, based on standardized advice sheets.

The results of this trial showed that, while there was some benefit to immediate antibiotics, delayed antibiotics was appropriate in the majority of cases. The group with the immediate antibiotic prescription exhibited shorter illnesses (-1.1 days, 95% confidence interval: -0.54 to -1.48), fewer nights disturbed (-0.72 nights, 95% CI: -0.30 to -1.13), and slightly less analgesic (paracetamol) consumption (-0.52 spoons per day, 95% CI: -0.26 to -0.79). However, there was no difference between the immediate and delayed groups in school absence, pain, or distress scores, since benefits occurred mainly after the first 24 hours when distress was less severe. In the delayed antibiotics group, only 24% of parents opted to give antibiotics to their child, 80% of the parents were very satisfied with the treatment, and fewer children had diarrhea (delayed 9%, immediate 19%, chi square 5.2, p=0.02). Parents in the delayed group believed less in the effectiveness of antibiotics and in the need to see the doctor with future episodes.

Conclusion and recommendations

Immediate antibiotic prescription provides modest symptomatic benefit compared to a delayed prescribing approach, and any benefit is mainly after the first 24 hours when symptoms are resolving. This must be balanced against the disadvantages of side effects and increasing parents’ belief in the importance of antibiotics. For children who are not very unwell systemically, a ‘wait and see’ approach is safe, feasible, very acceptable to parents, and results in a significant reduction in the use of antibiotic prescriptions for acute otitis media. Given the low analgesic use in most children, and common occurrence of night disturbance, doctors using the delayed approach should probably emphasize the importance of full doses of analgesics/antipyretics, particularly at bedtime.

References

Paul Little, MRC Clinician Scientist, Primary Medical Care, Community Clinical Sciences Division, University of Southampton, UK

Join the APUA 20th anniversary celebration at ICAAC on Sunday, September 23, 2001 from 6:30 to 8:00 PM in the Watertower Room at the Hyatt Regency Hotel in Chicago.

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APUA News

GAARD: A Global Surveillance Project

APUA implemented a public/private partnership, the Global Advisory on Antibiotic Resistance Data (GAARD), to develop a global databank to monitor trends in antibiotic resistance worldwide. As a pilot project, GlaxoSmithKline (Alexander program), Bristol-Myers Squibb (SENTRY), and Focus Technologies (TSN) contributed MIC data for Streptococcus pneumoniae, which was analyzed by APUA staff.

Over a three year period (1997-1999), the annual proportions of S. pneumoniae isolates not susceptible to penicillin were 29%, 28%, and 32% in SENTRY; 34%, 34%, 41% in Alexander, and 50%, 47%, and 44% in TSN. SENTRY and Alexander data suggested a trend toward higher non-susceptibility in 1999; that trend was statistically significant in the time necessary to document trends.

Based on the success of this pilot test, GAARD, with WHO and CDC as advisors, plans to invite new surveillance systems to join. By increasing the number of contributing data sources and providing a forum for expert analysis, GAARD will enable the analysis of trends, provide early warning, and answer specific public health questions. This will provide a valuable technical resource for policy makers, researchers, and health care providers.

New APUA Scientific Advisory Board members

APUA welcomes our new Scientific Advisory Board members:

- Alexander Tomasz, PhD, Plutarch Papamarkou Professor, Laboratory of Microbiology, The Rockefeller University, New York, US.
- Patrice Courvalin, MD, Professor and Head of Antibacterial Agents Unit and of National Reference Center for Antibiotics, Institut Pasteur, Paris, France.
- Jos WM Van der Meer, MD, Department of Internal Medicine, University Medical Center Nijmegen, Nijmegen, the Netherlands.

APUA Partnerships

APUA is partnering with Management Sciences for Health (MSH) to provide expertise in the area of antimicrobial resistance for the Rational Pharmaceutical Management (RPM) Plus Program. The USAID-funded program, an extension to the RPM Project, aims to improve the management of health commodities in developing countries to promote sustained access to and effective use of essential commodities and pharmaceuticals.

The American International Health Alliance (AIHA), in partnership with APUA, launched a Russian-language website with information on antibiotic use and resistance (www.eurasiahealth.org).

APUA Small Grants Program

An APUA-Ukraine study conducted by Drs. Igor Bereznjakov and O.S. Obukhova assessing antibiotic availability in the home was presented at the International Congress of Chemotherapy (ICC) in Amsterdam. Of 407 respondents, 78% reported having antibiotics at home. The antibiotics most often purchased without a prescription were trimethoprim/sulfamethoxazole, chloramphenicol and ampicillin. The most common reasons for purchase were cold, fever, cough and diarrhea. The APUA-Bulgaria study conducted by Drs. R. Markevska, T. Strateva, G. Gergova and E. Keuleyan, ‘Nasopharyngeal carriage of penicillin-resistant, macrolide-resistant and multiply-resistant Streptococcus pneumoniae in day-care centers in Sofia, Bulgaria’, and published in Clinical Microbiology and Infection, revealed that children colonized by penicillin and/or erythromycin-resistant pneumococci were more likely to have been treated with antibiotics during the previous 3 months than children carrying susceptible strains (p<0.001). APUA supported the antibiotic component of an intervention study conducted by APUA-Nepal chapter leader, Dr. K.K. Kafile, which aimed to increase awareness about drugs and their proper use among families through school children, teachers and women’s groups. The study found that educational efforts among women were most successful in increasing household knowledge. Professor J.S. Bapna and Dr. Rajeev Thakur completed their APUA-India study comparing sensitivity patterns and cost effectiveness of clinical isolates from hospitalized patients on newer antibiotics to those from patients on formulary antibiotics. As expected, treatment with non-formulary drugs was more expensive. Of the 50 isolates from patients on newer antibiotics, 29 were susceptible to one or more formulary antibiotics. However, sixteen of the 40 isolates from patients on formulary drugs were resistant to the prescribed formulary drug.
The Alliance for the Prudent Use of Antibiotics is a non-profit organization dedicated to curbing antibiotic resistance and improving the use of antibiotics throughout the world. Founded in 1981, APUA’s mission is to improve public health through education and research concerning antibiotic use and resistance. APUA’s resources include members in over 100 countries, numerous country chapters, an international scientific advisory board with members of national academies of medicine and science, and a professional staff with specialized expertise.

US Activities

This year the Centers for Disease Control and Prevention (CDC) and APUA strengthened their alliance to foster more careful use of antibiotics through developing a joint educational exhibit and sharing booth space at five major health care conferences. APUA Executive Director, Kathleen Young, was a panelist at CDC’s 2nd annual meeting of its National Antibiotic Use Campaign.

For the third year, Procter and Gamble provided APUA an unrestricted grant for activities geared toward education of US primary care practitioners concerning guidelines for antibiotic use. These funds will support another six Health Provider Lectures in which infectious disease physicians present diagnostic and treatment guidelines at major conferences of primary care physicians and nurse practitioners.

APUA, CDC, American Academy of Family Practitioners (AAFP) and other official partners have joined in a national campaign with the Coalition for Affordable Quality Healthcare (CAQH), a group comprised of 24 of the largest US managed care companies. In addition to its national campaign, CAQH is conducting three major pilot studies to determine the best ways to educate health care providers. APUA Vice President, Thomas O’Brien, MD, participated in the inaugural press conference to raise awareness about antibiotic use. Dr. Stuart B. Levy contributed an educational piece for the physician newsletter of these plans.

The American College of Physicians-American Society of Internal Medicine (ACP-ASIM) and APUA are working together to increase awareness about appropriate antibiotic use. Dr. Vincenza Snow of ACP-ASIM wrote an article on its recently released antibiotic guidelines for adult respiratory illnesses for APUA’s newsletter. APUA President Dr. Stuart B. Levy will address attendees at the ACP-ASIM annual meeting in April 2002 in Philadelphia.

APUA Chapter News

APUA-Korea, with support from the Asan Foundation, is planning its inaugural meeting in November. Dr. Changgi Hong, President of the Asan Medical Center in Seoul, will lead the chapter and Dr. Yang Soo Kim will serve as Coordinator. Dr. Donald Lyon, from the Dept. of Microbiology, Prince of Wales Hospital, is working to develop an APUA-Hong Kong Chapter. APUA-China, headed by Dr. Wang Fu, Institute of Antibiotics in Shanghai, is organizing a conference on infection and antimicrobial chemotherapy at the end of September. Dr. Roman Kozlov, APUA-Russia Chapter Coordinator, recently became the first International Ambassador in Eastern Europe for the American Society for Microbiology. Dr. Fernando Baquero (APUA-Spain) and Dr. Giuseppe Cornaglia (APUA-Italy) chaired a Society Symposium at the ICC on 'Antibiotic use and resistance in selected countries: prescription patterns and surveillance.' Dr. Helen Giamarellou (APUA-Greece), Dr. Leonid Stratchounski (APUA-Russia), Dr. Otto Cars (APUA-Sweden), and Dr. Anibal Sosa (APUA Latin America Initiative) also participated.