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Develping Country Perspective: Probiotics With or Without Antibiotics

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An Introduction to this Issue

Paulami Naik and Bonnie Marshall
Alliance for the Prudent Use of Antibiotics

A healthy human intestinal tract hosts 10 times as many bacteria, as there are cells in the human body. Represented in this population are 400 to 1000 bacterial species distributed among nine phyla. [1,2] These bacteria provide us with energy through fermentation, produce vitamins for our needs, protect us from infection, and ensure proper functioning of our immune system. [3] The specific distribution of bacteria that colonizes our gut at any given time can have an important effect on our health and it can be manipulated with the use of "probiotics" and "prebiotics".

Probiotics are "live micro-organisms that confer a health benefit on the host when consumed in adequate amounts." [4] The most commonly used and best studied probiotics are species of the bacteria *Lactobacillus*, *Bifidobacteria*, and *Streptococcus* and the yeast *Saccharomyces boulardii*—typically delivered singularly or in combination via various yogurt preparations, or as supplemental capsules. Less frequently, whole fecal transplants from healthy donors are utilized as suppositories. Often discussed in relation to probiotics are non-live "prebiotics". Prebiotics are "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improve host health." [5] In this issue of the APUA Clinical Newsletter, we focus solely on probiotics.

The first formal research on probiotics dates back to the early 1900s. In 1907, Russian Nobel laureate, Dr. Elie Metchnikoff published The Prolongation of Life in which he noted that exceptionally long-lived Bulgarian peasants, consumed large quantities of sour milk containing *Lactobacillus bulgaricus*. He wrote, "The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes." [6] Through this work he established a foundation for the study of probiotics.

With the advent of antibiotics, the interest in probiotics lay largely dormant for several decades. However, with the resurgence of interest in the gut flora, the previous 15 years have witnessed significant advances in the characterization of select gut probiotic strains and on substantiation of their health claims. Current investigations into the human microbiome, such as the work of the National Institute of Health's Human Microbiome Project, are revealing the complexity of the organisms inhabiting the human body. Dr. Martin Blaser, professor of microbiology at New York University, and investigator of the link between gut flora and obesity states, "We're still learning how far the impact of the microbiome reaches and the costs of perturbing it." [7] The interest in the micro biome has advanced the probiotic field as individual strains and functions are being researched. Nonetheless we are still on the frontiers of understanding their specific roles and potential uses. Molecular and genetic studies are making significant advances in understanding the mechanistic basis underlying the benefits s of probiotic strains.

Relation to Antibiotic Resistance

Continued or excessive use of antibiotics is known to disrupt the normal micro biota of the human body. Promptly restoring normal balance of flora following treatment is important for preventing unrestrained overgrowth of undesirable, multidrug resistant strains such as *Clostridium difficult* and other hospital acquired opportunists. Probiotics have emerged as a valuable adjunct to antibiotic therapy and as a useful tool in avoiding or reducing antibiotic use. Given the recent decline in the development of new classes of antibiotics and the increase in multi-drug resistant superbugs, the

search for additional approaches for treatment and prevention of bacterial disease is increasingly urgent.

Probiotic Use and Safety

Probiotics are widely considered to be safe for human oral and vaginal use and there is a long history of the use of fermented milk products with minimal recorded reported side effects. The number of probiotic products available on the world market is estimated to be over 2000 [8], but the industry remains largely unregulated and unstandardized—making comparative studies difficult. To begin filling this void, scientists have formalized groups such as the International Scientific Association for Probiotics and Prebiotics (ISAPP), a non-profit founded in 2002 to raise the scientific credibility of the field by working with experts and conducting meetings on high quality research. By providing an objective, science-based voice, ISAPP hopes to benefit the end users of these products by helping them make informed choices. [9] ISAPP has endorsed the guidelines set by the World Health Organization (WHO) and the United Nations Food and Agriculture Organization (FAO) for evaluation of probiotics—governing, strain designation, efficacy/effectiveness and safety. [4,10] For example, new strains and products should be proven safe in human studies amend those bearing some limitations, (such as use of *S. boulardii [S. cerevisiae*]) in patients with a leaky gut or other risks) should be clearly labeled. [11]

In the United States, probiotics are currently classified as "dietary supplements", (not "drugs") and as such, the Food and Drug Administration (FDA) only requires premarket notification, with no demonstrations of safety and efficacy required. [12] Due to their overall safety, guidelines for use of probiotics in the hospital are generally lacking, although some caution is advised for use in certain disease states (e.g., severe colitis, bowel leaks, neutropenia) where the potential exists for the probiotic to enter the blood or peritoneum. [13] Likewise, special care should be taken by healthcare personnel who handle both probiotic capsules and venous catheters in order to avoid transfer to the bloodstream. [12] Of more recent interest and concern are safety considerations relating to transferable genetic elements that may confer antibiotic resistance from the probiotic to pathogenic strains, or even to the commensal flora. [14]

Current Applications and Future directions

To date, only a very few probiotic strains are well researched and tested and most relate to interventions in diarrheal illness. Confounding factors in clinical trials have undermined and limited the ability to clearly determine efficacy for other strains and infectious disease states. Fewer supporting studies exist in the area of respiratory disease, but probiotics may offer some promise in treating sinusitis, bronchitis, and pneumonia. The current lack of rapid diagnostics for upper respiratory illness (URI) has led to considerable overuse of antibiotics in this area and there is a large potential for probiotic intervention. A recent Cochrane meta-analysis of 10 clinical trials concluded that probiotic intervention exceeded the placebo in reducing episodes of acute URI, with some more limited evidence that probiotics could reduce the prescription of antibiotics. [15]

In this issue of the APUA Newsletter, current as well as future probiotic applications are examined. Tufts University Schools of Nutrition and of Medicine are at the forefront of probiotics research and some of their experts have contributed articles to this issue. Drs. Barry Goldin and Sherwood Gorbach, co-discoverers of Lactobacillus GG–the first probiotic proven to colonize the gastrointestinal tract—offer an overview of the current and proposed uses of probiotics and evaluate the strength of supporting evidence. Dr. Shira Doron reviews the use of probiotics for prevention and treatment of gastrointestinal diseases. Interesting perspectives from research in developing countries are provided by Dr. Gregor Reid of Western University in Canada and Drs. Christine Wanke and Honorine Ward of Tufts Medical School, who examine probiotics as useful interventions in the vicious cycle of malnutrition and infectious disease that severely undermines childhood development.

In their recognition and endorsement of probiotic therapy, the United Nations and World Health Organization, issued the call for "Efforts…to make probiotic products more widely available, especially for

relief work and populations at high risk of morbidity and mortality". This call has yet to be ratified by government agencies and multinational probiotic companies. With the looming global crisis in antibiotic resistance, and a dearth of new antibiotics in the pipeline, there persists a critical need for adjuncts and alternatives to antibiotic therapy that will aid in preserving our severely compromised antibiotic treasures. With their prospects of enhancing antibiotic efficacy, alleviating antibiotic side effects, and even reducing or eliminating the need for antibiotics, coupled with low cost and relative accessibility, probiotics offer promise in filling this void, but clearly, better designed, more rigorous studies are needed to optimize their full potential as interventions, with or without antibiotic therapy.

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Clinical Indications for Probiotics: An Overview

The following article was extracted with permission from a publication of the same title which originally appeared in Clin Infect Dis. 2008. 46 (l 2): S96-S100. This reprint has been updated with new references (see Refs 45-48.)

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Probiotics have been defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host". [1] Probiotics have been used to treat a wide range of diseases, ailments, and conditions that affect humans and animals. Additional medical applications have been proposed for potential future uses, depending on the outcomes of future experimental studies. The clinical uses of probiotics are broad; however, the clinical indications based on evidence-based studies are much narrower and are open to continuing evaluation. Table 1 contains a partial list of human diseases and conditions that probiotics have been used to prevent and/or treat.

The current and proposed uses of probiotics cover a wide range of diseases and ailments. An attempt has been made to classify the quality of evidence that supports these various applications. [44] These classifications are based on existing studies, most of which are cited in this article, and not on an exhaustive review of the entire literature on probiotics. The broad classifications include (Table 2) applications with proven benefits, applications with substantial evidence that require additional support, promising applications that need substantial additional evidence, and proposed future applications.

Proven benefits of probiotics include the treatment of acute and antibiotic-associated diarrhea; applications with substantial evidence include the prevention of atopic eczema and traveler's diarrhea; promising applications include the prevention of respiratory infections in children, prevention of dental caries, elimination of nasal pathogen carriage, prevention of relapsing *C. difficile*–induced gastroenteritis, and treatment of inflammatory bowel disease; and proposed future applications include the treatment of rheumatoid arthritis, treatment of irritable bowel syndrome, cancer prevention, prevention of ethanol-induced liver disease, treatment of diabetes, and prevention or treatment of graft-versus-host disease.

The use of probiotics in medical practice is rapidly increasing, as are studies that demonstrate the efficacy of probiotics. A note of caution should be applied:

Table 1. Medical applications in humans for different classes of probiotics.

Medical condition	Class(es) of probiotic	References
Lactose maldigestion	LAB and *Streptococcus Salivarus* subsp. *thermophilus*	[2-5]
Gastroenteritis		
Acute diarrhea	LAB, *Bifidobacterium* species or *Saccharomyces boulardii*	[6-17]
Antibiotic-associated diarrhea	LAB or *S. boulardii*	[18-24]
Traveler's diarrhea	LAB	[25,26]
Allergies	LAB	[27-31]
Clostridium difficile-induced colitis	LAB	[32-34]
Dental caries	LAB	[35]
Intestinal inflammation in children with cystic fibrosis	LAB	[36]
Respiratory infection in children	LAB	[37]
Nasal colonization with pathogens	LAB	[38]
Inflammatory bowel disease or irritable bowel syndrome	LAB	[39-43]

NOTE. LAB, lactic acid bacteria

Table 2. Present and future clinical applications of probiotics, by level of evidence of efficacy

Applications with strong evidence
- Gastroenteritis
  - Acute
  - Antibiotic associated

Applications with substantial evidence of efficacy
- Allergic reactions, specifically atopic dermatitis

Applications that have shown promise
- Childhood respiratory infection
- Dental caries
- Nasal pathogens
- Relapsing *Clostridium difficile*-induced gastroenteritis (prevention)
- Inflammatory bowel disease

Potential future applications
- Rheumatoid arthritis
- Irritable bowel syndrome
- Cancer (prevention)
- Ethanol-induced liver disease
- Diabetes
- Graft-versus-host disease

negative findings are being reported, as would be expected as more studies are being performed and as more applications are being sought for the use of probiotics.

Overall, probiotics appear to be here to stay as part of the physician's armamentarium for the prevention and treatment of disease; however, more evidence-based research is required to firmly establish medical areas of use and areas in which probiotics are not applicable.

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Probiotics for the Treatment and Prevention of Gastrointestinal Disease

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Gut bacteria

The bacteria in our gastrointestinal tract have an important effect on our health. The intestinal microbiota can be altered by such interferences as a course of antibiotics, or an episode of intestinal infection. Aberrant gut microbiota have been demonstrated not only in diarrheal diseases, but also in inflammatory bowel disease, irritable bowel syndrome and even in diseases which manifest outside the gastrointestinal tract. [1]

Probiotics

Living microorganisms have long been used as supplements to restore gut health at times of dysfunction. They do so not only by changing the intestinal microbiota, but also by their immunomodulatory effects as well as elaboration of antibacterial substances.

A probiotic is "a live microbial food ingredient that, when ingested in sufficient quantities, exerts health benefits on the consumer". [2] To be considered a probiotic, a bacterial strain must be of human origin and safe for human use. Genera represented in this category include lactobacilli, bifidobacteria, streptococci, and enterococci. There are many probiotic strains, each with unique characteristics. These have been studied for use in the treatment and prevention of a wide range of diseases.

Treatment and prevention of acute diarrhea

Several meta-analyses and systematic reviews have been written on this topic and have found probiotics to be effective. [3-7]

Lactobacillus rhamnosus strain GG (LGG) and *Lactobacillus reuteri* have been the most commonly studied probiotics for use in the treatment of acute diarrhea in children. [7] The largest study of LGG for acute diarrhea in children was conducted by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2000. In this study, 287 children in ten countries ages 1 to 36 months admitted with moderate to severe diarrhea were randomized to receive either LGG or placebo along with standard oral rehydration solution. The patients who received LGG had a shorter duration and decreased severity of illness, had a shorter hospital stay and were less likely to have persistent diarrhea. [8]

Shornikova *et al* performed two smaller studies, one randomizing 86 children and one randomizing 40 children ages 6 to 36 months to *Lactobacillus reuteri* or placebo. The duration of watery diarrhea was decreased in the treated group, as was the percent of subjects with persistent diarrhea on day two of illness and the frequency of diarrhea on day two. Colonization of the intestine by *Lactobacillus reuteri* was confirmed by stool culture. The larger study, which had higher and lower dose arms, also showed a correlation between the dosage of *L. reuteri* and the clinical effect. [9,10]

Prevention of antibiotic-associated diarrhea and gastrointestinal side effects

Antibiotic-associated diarrhea (AAD) is diarrhea that occurs during or shortly after administration of an antibiotic, with no other known cause. The frequency of occurrence varies with the antibiotic, but is estimated to occur in approximately 25% of the patients receiving antibiotics. The rate of AAD in children may be less, as little as 11% in one study, where it was found to be

highest (18%) in children under the age of two years. [11]

McFarland conducted the largest meta-analysis to date evaluating 25 randomized controlled trials of probiotics for the prevention of AAD including 2810 subjects. [12] Of these, 13 (52%) demonstrated a significant reduction in the incidence of AAD in the probiotic-treated group compared with the placebo group. Among the studies on adults, only 44% had a reduction in AAD in the probiotic group, while 67% of the pediatric studies reported a benefit in the probiotic group. Many different probiotic strains were used in these trials, including several probiotic mixtures, and at various doses. When these analyses were stratified by probiotic strain, only *Lactobacillus rhamnosus* GG, *Saccharomyces boulardii* and the various probiotic mixtures had significant efficacy.

"Given the current state of antimicrobial resistance and stagnating antimicrobial drug development, it is critical to look to antibiotic alternatives such as probiotics to treat and prevent infections."

Prevention of travelers' diarrhea

Diarrhea occurs in 30% to 50% or more of travelers to developing countries. [13] There have been a number of studies on the use of probiotics for the prevention of travelers' diarrhea and the results are conflicting. The largest was a Finnish study that randomized 756 subjects traveling to two resorts in Turkey to take Lactobacillus GG or placebo during their stay abroad. The results from subjects at one of the resorts were not statistically different between groups, while at the other resort, the LGG group had a statistically significant protection rate of 39.5% in the first week and 27.9% in the second week. [14]

***Helicobacter pylori* infection**

Helicobacter pylori is responsible for such conditions as gastritis, peptic ulcers, and gastric cancer. It colonizes the epithelial cells of the stomach and is capable of penetrating these cells. *In vitro* studies have demonstrated that various strains of *Lactobacillus* have antibacterial activity against *H. pylori* [15, 16] and animal studies have shown their ability to prevent *Helicobacter* infection and colonization [15, 17-19] and to attenuate gastritis. [19]

Lactobacillus acidophilus decreases the viability of *H. pylori* as well as its binding capacity to human mucosecreting cells *in vitro*. Probiotics have also been shown to inhibit urease activity of *H. pylori* both *in vitro* and in the mouse stomach. [15] Human studies have demonstrated various effects of probiotics on *H. pylori* infection. Studies have shown a decrease in urea breath test values after treatment with probiotics. [20-23] Wang *et al* showed reduced *H. pylori* density and gastritis severity in antral biopsies. [20]

More recent studies have focused on probiotics as adjunctive therapy to improve the rate of *H. pylori* eradication with standard multi-drug therapy. Sykora *et al* studied 86 symptomatic *H. pylori*-positive children who were randomized to omeprazole, amoxicillin and clarithromycin plus or minus fermented milk containing *Lactobacillus casei* DN-114 001. There was a significantly enhanced therapeutic benefit with the addition of the probiotic from 61% to 92%. [24] Sheu *et al* studied 138 adults who had failed standard triple-drug therapy for *H. pylori*, randomizing them to pre-treatment for four weeks with yogurt containing *Lactobacillus acidophilus* La5, *Lactobacillus bulgaricus*, and *Bifidobacterium lactis* Bb12 or no pre-treatment followed by quadruple therapy with omeprazole, amoxicillin, metronidazole and bismuth subcitrate. There was a significantly higher eradication rate in the pre-treated group (86% versus 71%). [25] On the other hand, in a study of 65 children who tested positive for *H. pylori* in Argentina treated with standard triple therapy followed by three months of yogurt (with *Lactobacillus casei* and *Bifidobacterium animalis*) or milk placebo, no differences were seen in the eradication rates at one and three months. [26]

Treatment and prevention of *Clostridium difficile*

Clostridium difficile infection can cause a spectrum of disease ranging from subclinical infection to severe disease including profuse diarrhea, colitis, toxic

megacolon and death. The disease generally responds to therapy with antibiotics but recurrences are common and develop in up to one third of patients. These recurrences can be refractory to therapy. Dendukuri *et al* conducted a systematic review on the use of probiotics for prevention and treatment of *C. difficile*-associated diarrhea (CDAD) in adults. [27] Four randomized controlled studies were identified with CDAD as the primary outcome. Four additional randomized controlled studies identified CDAD as a secondary outcome. Strains studied included *S. boulardii* in 5 of the studies, and different strains of *Lactobacillus* in the other three, one in combination with *Bifidobacterium*. In these studies, probiotics did not have a significant effect on the prevention of CDAD, and only two studies showed a benefit for probiotics in treatment of CDAD, particularly in patients with more severe disease, however the variability in the use of concomitant antibiotics against *C.difficile* make interpretation of the results difficult.

In conclusion, there is considerable need for many more well designed trials to be conducted before we can fully understand the benefits of probiotics in the treatment and prevention of gastrointestinal diseases. Each strain must be studied individually for its efficacy in each disease state, since results from the study of one strain cannot be extrapolated to another. Given the current state of antimicrobial resistance and stagnating antimicrobial drug development, it is critical to look to antibiotic alternatives such as probiotics to treat and prevent infections.

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Develping Country Perspective: Probiotics With or Without Antibiotics

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When I read an article on the BBC online news on November 19th, 2004 stating that the World Health Organization and Unicef was recommending daily use of trimethoprim-sulfamethoxazole for every HIV-positive child in Africa, I somewhat despaired at society's approach to disease management. It had been 13 years since we had shown that 7 days of antibiotic therapy could disrupt the beneficial vaginal microbiota for over six weeks [1], and nine and a half years since the British Parliament debated the deaths, injuries and other side-effects of trimethoprim-sulfamethoxazole. While this combination is effective at treating many infections, the thought that two respected organizations were advocating 40 billion doses to children per year seemed madness. Given Martin Blaser's recent Nature article highlighting the folly of overuse of antibiotics and the critical importance of the host's beneficial microbes [2], my advocacy of alternative approaches seems justified.

In hindsight it is ironic that in the same year, 2004, we launched a program in Tanzania whereby local mothers ('mamas') would produce a yogurt supplemented with probiotic *Lactobacillus rhamnosus* GR-1, with the aim of improving the quality of life of HIV-positive children and adults (Figure 1). [3] The yogurt contains about 9 g of protein per serving yielding >15% of the recommended daily allowance and 8 g of fat per serving. It is a rich source of many micronutrients, including zinc, phosphorous, calcium (33% of daily recommendation), pantothenic acid, vitamin B_{12} (>40% of daily recommendation), riboflavin and vitamin A (10% of daily recommendation). [4] Such is the enthusiasm for the program, that the communities have helped set up another 11 kitchens in Tanzania and Kenya with more planned there and in Rwanda, Burundi and Malawi. To date, these have employed over 60 mamas and farmers, been host to 55 student interns from Western University in Canada, and led to 26 publications on various aspects of the project. In addition, over 20,000 students at Western have been engaged in fund raising and dissemination of the project.

Whilst such engagement in Africa is laudable, are there health benefits associated with the yogurt intake? Answering this required setting up research collaborations with various partners, in particular the National Institute for Medical Research in Mwanza, and performing studies with essentially no funding from Canadian government granting agencies. Nevertheless, interesting findings have emerged with administration of yogurt and capsules containing *L. rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14.

The first study followed 49 male and female adults (age 35–45), with 29 receiving the probiotic yogurt (250 mL daily for 30 days) and 20 not. Five in each group were taking anti-retroviral therapy (ART). Compliance was good, but on average, participants still missed 3–5 days yogurt, due to being too sick to travel, lacking a family member to assist with program adherence, or fear of domestic violence against women who were leaving the home to get yogurt. Almost all of the participants had marked improvements in their weight, and eight showed an improvement in their weight category, moving from severely to moderately underweight or from moderately underweight to mildly underweight. Significant increases were noted in thiamin, riboflavin, biotin, vitamin C, pantothenic acid, calcium ($p < 0.0001$), copper, phosphorus and potassium. Based upon self-perceptions and physician diagnoses, consumers of the probiotic yogurt had significantly fewer fungal conditions over the

time period of 60 days [$r = 0.417$, $n = 49$, $p < 0.01$], fewer episodes of diarrhea [$r = 0.372$, $n = 49$, $p < 0.01$], and substantially lower degree of fatigue [$r = -0.365$, $n = 49$, $p < 0.01$]. This was the first evidence that the yogurt might act as a prophylactic against infection.

The finding has been further supported by an observational study. [5] In addition, the prophylactic effect in reducing urinary tract infection (UTI) recurrences has been confirmed with strains GR-1 and RC-14 in capsules administered to elderly Dutch women for one year [6], and with *Lactobacillus acidophilus* given to South Korean children with vesicoureteral reflux [7], both compared to trimethoprim-sulfamethoxazole. Of importance, the GR-1/RC-14 treatment resulted in no drug resistance changes compared to the antibiotic treated group in whom resistance to trimethoprim-sulfamethoxazole, trimethoprim, and amoxicillin increased within only one month from 20%-40% to 80% -95% in *E. coli* from the feces and urine. [6] Likewise, in the study of children, sensitivity of *E. coli* to trimethoprim-sulfamethoxazole was 57.1% in the probiotic group and reported as zero in the antibiotic group ($P<0.019$). [7] Such results clearly indicate the flaw in the WHO/Unicef approach and the need to retain antibiotics for curing infection rather than preventing them. Moreover, the findings indicate that probiotics need to be included in discussions on how to prevent infant deaths from HIV in Africa. Rather than forcing African children to take a developed world antibiotic every day resulting in that agent no longer being able to cure infection because of resistance, would it not make more sense to create locally driven initiatives that take advantage of available food sources, stimulate self-empowerment and deliver fairly similar disease prevention?

The advantages can potentially extend beyond preventing infection. One study of 40 patients showed superior cure of bacterial vaginosis (BV) with intravaginal probiotics versus metronidazole. [8] Studies in Nigeria and Brazil have shown that combining *Lactobacillus* GR-1 and RC-14 with antimicrobials can improve cure of vaginal infections. [9-12] The effect appears to involve creating an environment that restores the indigenous lactobacilli as the dominant organisms, while in the case of *Candida*, suppressing fungal growth, increasing expression of stress-related genes, lowering expression of genes involved in fluconazole resistance [13] and up-regulating IL-8 and IP-10 secretion. [14] This is a good example of using beneficial organisms to counter pathogenic ones. Other examples of this phenomenon have been published. [15,16]

A clinical study using *Lactobacillus crispatus* CTV-05 administered intravaginally following metronidazole therapy, showed that an ability of the organism to persist on the mucosa was associated with significant reduction in BV pathogens, *Gardnerella* and *Atopobium*. [17] In a randomized, placebo-controlled trial study of HIV-positive children, daily use of formula containing *Bifidobacterium bifidum* with *Streptococcus thermophilus* increased the mean CD4 count (+118 cells mm(-3)) compared to -42 cells mm(-3) for children receiving control formula ($p = 0.049$) (791 cells mm(-3)). [18]

In summary, the current medical approach to managing infection remains too focused on traditional antimicrobial agents and protocols, disregarding their side effects and increased resistance. New agents are long overdue for conditions such as UTI and BV and for patients with chronic diarrhea. Probiotics certainly warrant consideration to manage infections and

Figure 1. The Tukwamuane Women's Group whose Mabatini kitchen in Mwanza, launched the Western Heads East probiotic yogurt initiative, with production beginning in January 2005.

potentially also improve antimicrobial efficacy. The social business model used in Africa should be considered in the so-called developed world, where poverty, access to adequate care, and poor nutrition all contribute to infections continuing to cause widespread morbidity and mortality. The success obtained from fecal transplant in curing *Clostridium difficile* caused mostly by antibiotic eradication of the gut microbiota [19], suggests that the types of probiotics that will be used in the future will be different in form and delivery from the present. Such a change needs to be aligned with major alterations to how probiotics are regulated, and in creation of a system understood by lay people as well as policy makers. [20] With few side effects and excellent patient compliance, HIV positive patients are asking why are more foods not targeted to reduce the burden of disease? [21]

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Probiotics for Diarrheal Disease and Malnutrition in Children in Resource-Poor Countries

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The vicious cycle of infectious diarrheal disease and malnutrition is responsible for significant morbidity and mortality in children under the age of five years, particularly those from low and middle-income countries. A recent analysis of child mortality in 2010, estimated that worldwide about 60% of the 6.7 million deaths that occur in children under the age of five years are caused by infectious diseases and that about 10% are due to diarrhea. [1, WHO] Malnutrition is estimated to contribute to over one third of child deaths. In 2010, about 20 million children worldwide were estimated to suffer from severe acute malnutrition, 171 million children below five years of age were stunted, and 104 million were underweight. [WHO]

While malnutrition may occur throughout the childhood years, it may be presumed that loss of weight or inability to grow may have more of an impact the earlier it occurs. Such early malnutrition may be referred to as growth faltering. There is no clear definition of growth faltering, but it is widely assumed to begin around the time of weaning in low and middle income countries and is generally assessed by weight-for-age (WAZ), height-(or length)-for age (HAZ) and weight-for-height (WHZ) Z scores. [WHO] An analysis of the WHO Global Database on child growth and malnutrition of 39 nationally representative data sets from recent growth monitoring programs in developing countries [2] found the following: For children in the developing world at birth, in comparison to the National Center for Health Statistics (NCHS), the average weight-for-age, length-for -age, and weight-for-length are quite close to the reference. Growth faltering then occurs, so that by 18 months, mean weight-for-age values and mean length-for -age values are between 1 and 2 standard deviations below the reference median value.

The three primary growth parameters (WAZ, HAZ, WHZ) show different patterns. Mean weight starts to falter about 3 months of age, and declines rapidly until 12 months. Between 12 and 19 months this decline slows. Most wasting (assessed by WAZ score) in children occurs in the period between 3 to 15 months of age. For length, although the mean birth values are close to the NCHS standard, faltering starts soon after birth and lasts well into the third year, and is not recovered thereafter. These processes appear to be independent of each other and the pattern is remarkably similar in multiple developing countries.

Current recommendations are that weaning occurs from 4-6 months onward, as foods other than breast milk are introduced into the diet. [3, 4] Initiation too early displaces breast milk, decreases mother's milk production and results in malnutrition, while weaning too late leads to growth faltering and depressed immune function. Regardless of the timing, in situations where environmental contamination is high, weaning exposes the infant to high levels of enteric pathogens and increased morbidity and mortality secondary to infectious disease and malnutrition. Multiple studies from developing countries have shown that diarrheal disease significantly increases at about 6 months of age, secondary to increased exposure of the infant to pathogens as a result of weaning initiation. [3-6]

Contamination of water is common and this water is used in preparation of weaning foods. Contamination of foods after cooking also occurs.

A malnourished child or a child who is frequently exposed to enteric pathogens is at higher risk of developing diarrheal disease. [7-11] Recent studies suggest that acute watery diarrhea accounts for perhaps one third of all deaths from diarrhea and dysentery for another 20%. Persistent diarrhea (PD) is the greatest problem, accounting for approximately 45% of childhood deaths from diarrhea. [5, 12, 13] A malnourished child is at increased risk for an episode of acute diarrheal disease to become prolonged. [14] In spite of the fact that only 10 -16% of episodes of acute diarrhea progress to PD, the mortality associated with PD is disproportionately high. [12, 13] Malnourished children with PD had a higher risk of death from PD than better-nourished children within the same community. [15] There is also evidence that children who develop PD are subsequently at risk for more episodes of diarrhea than children who have never had an episode of PD. [13, 16-18]

"Thus, interventions such as probiotics may be most effective during pregnancy and the first two years of life, the so-called "first 1000 days" and may need to target pregnant women in addition to their infants. "

Probiotics are viable bacteria, which colonize the intestine and modify the intestinal miroflora and their metabolic activities with a beneficial effect for the host. [19-21] *Lactobacillus rhamnosus*, strain GG (LGG) (ATCC 53013), is an extensively studied probiotic strain. LGG has been used as therapy in several randomized, placebo-controlled trials of acute pediatric diarrhea with success. [22-25] LGG has been proven successful in decreasing the duration of childhood diarrheal illnesses for which the pathogen was not known, in studies done in the developing world. In Northern Pakistan, LGG was shown to significantly reduce the duration of acute diarrheal illness in hospitalized children compared to those treated with placebo. [26] LGG was able to significantly reduce the duration of acute watery diarrheal illnesses in children in Thailand when compared to placebo. [27] LGG has also been effective in treating diarrhea caused by *C. difficile* in children and in elderly adults with relapsing diarrhea [28, 29, 50-52]. Likewise, it has been used to prevent diarrhea. A study of the ability of LGG to reduce diarrhea in undernourished Peruvian children suggests that there were fewer episodes of diarrhea in the children who received the probiotic. [55] Additionally, LGG has also been shown to enhance the immunogenicity of oral vaccines. [30]

Other studies of LGG suggest that it permits healing of the intestinal mucosa by reducing gut permeability and by enhancing local intestinal immune responses as well as by reconstituting the intestinal flora. [31-33] Although the effect of LGG on growth faltering and malnutrition has not been extensively studied, the beneficial impact of LGG on intestinal integrity and the ability of LGG to reduce the total days of diarrhea are the basis for the hypothesis that LGG will reduce the incidence of growth faltering. The microbial communities in the gastrointestinal tract consist of over 1000 species and outnumber human cells tenfold. [34] These communities, known as the "microbiota" and their collective genomes, the "microbiome", play a major role in maintaining gut homeostasis, contributing to nutrition and promoting resistance to infection by preventing colonization with pathogens, modulating innate and adaptive immune responses, preserving intestinal mucosal integrity, controlling inflammation and contributing to nutritional status. Perturbation of the intestinal microbiota is associated with impaired nutritional and immune status, increased susceptibility to infection, and adverse clinical outcomes. Culture-independent and other high throughput technologies, including next generation sequencing and mass spectrometry, have enabled rapid and accurate characterization of the intestinal microbiome, metagenome, metatransciptome and metabolome in various physiological as well as pathological states, such as obesity and inflammatory bowel disease.

Recently, alterations in the intestinal microbiota and their metabolic activities have been implicated as playing

a role in malnutrition as well as in environmental enteropathy in children in developing countries. [35, 36] Although further studies need to be done to confirm this possibility, this finding raises the possibility that in addition to provision of adequate quantity and quality of nutrients, restoration of the gut microbiome to a more "healthy" state with the use of tailored probiotics [34, 37-8] may have a beneficial effect on malnutrition and growth faltering in children in resource-poor areas. Stunting in these children occurs very early in life and is thought to be initiated during pregnancy and intrauterine growth. Thus, interventions such as probiotics may be most effective during pregnancy and the first two years of life, the so-called "first 1000 days" and may need to target pregnant women in addition to their infants.

Thus far, probiotic approaches have employed single, or a combination of a few, beneficial bacterial species. However, the likelihood that multiple microbes are involved in contributing to the health of the microbiome and the recent success of "fecal transplants" [39] suggest that these approaches may need to be customized to include multiple microbes with defined metabolic activities for specific disease states. The use of "designer" probiotics that are engineered to block deleterious receptor-ligand interactions of pathogenic organisms with host cells [40] may also be useful to target enteric infections that contribute to the vicious cycle of infectious diarrhea and malnutrition.

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Report from the Field: Antibiotic stewardship in Bulgaria – achievements and further needs

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Antibiotic Regulation

In Bulgaria, the Ministry of Health (MH) is the main regulator and the Bulgarian Drug Agency (BDA) is responsible for drug licensing and control. In order to be introduced to the market, an antibiotic needs an application and assessment. This procedure is based upon EU rules and the license lasts five years. The MH organizes a Commission to select drugs to be bought and reimbursed by the National Health Insurance Fund (NHIF).

One achievement in 2010 was the strengthening of control by the BDA on over-the-counter sales of antibiotics through inspections and penalties. But because the industry perceives Bulgaria's market as unattractive, important antibiotics such as the group of penicillinase-resistant penicillins, colistin, amphotericin B and nitrofurantoin are lacking. For example, nitrofurantoin is not licensed in Bulgaria and patients must travel abroad and buy the drug from Greece or Turkey.

Finally, there is one new option in the 2011due to the changes in the Law for Drugs for Human Usage. The hospitals may now apply for antibiotics not available on Bulgarian market— if they have been licensed in other EU countries, and if the hospitals can provide data that no alternatives are available.

Another important issue is the price of antibiotics. It was found that many drugs imported or produced by Bulgarian manufacturers are being sold in Bulgaria at higher prices than in the other countries. This question was recently considered by the new Minister of Health and the president of the NHIF.

Antimicrobial Resistance Surveillance

The National Antimicrobial Resistance Surveillance (ARS) in Bulgaria dates back to 1998. A National Reference Laboratory on Quality Control in Microbiology and Antimicrobial Resistance Surveillance was created at the National Center for Infectious and Parasitic Diseases. The Laboratory organizes external laboratory control twice a year and contributes to the standardization of antimicrobial susceptibility testing. Microbiology laboratories in Bulgaria mandatorily participate in the ARS system BulSTAR. Some hospital laboratories also participate in the European Antimicrobial Resistance Surveillance Network (EARS-Net) project coordinated by the European Centre for Disease Prevention and Control (ECDC). Many have

Table 1. Hospital antibiotic consumption in Sofia, Bulgaria

Year	Alexander's University Hospital[1]	Medical Institute, Ministry of the Interior[2]	Multi-profile Hospital[3]
2001	25	29.7	
2002	20	45.9	
2003	23	42.8	
2004	28	46.2	
2005	30	51.8	
2006	27.5	44.5	40.2
2007	30	54.0	35.8
2008	37	26.7	41.3
2009		44.1	41.9
2010		49.9	40.1
2011			36.3

Units: DDD/100-bed-day
1. Indiscriminated use of ceftriaxone (since 2006) represents 99% of the 3rd generation cephalosporins and accounts for ~50 % of systemic antibiotics.[1]
2. Rank of antibiotic groups, 2010 in DDD/100 bed-day:
penicillins – 11.1, cephalosporins – 17.4 , penems – 0.3, MLS – 4
aminoglycosides – 3.2, fluoroquinolones – 4.0,
glycopeptides – 0.2, imidazoles – 3.0
3. Relative antibiotic group use: penicillins:10-43 %, cephalosporins: 13-42 %, MLS: 6-8 %, fluoroquinolones: 10-12 %, aminoglycosides: 4-9%, others:1-3 %. [3]

traditions in ARS: they collect, analyze and interpret hospital ARS data and periodically publish booklets, with informational and educational content, that serve policy-makers. [1,2] The most problematic resistant organisms in Bulgaria are the ESBL-producing *Enterobacteriaceae* and multidrug-resistant non-fermenters.

Antibiotic Consumption

Most of the laboratories that participated in the Antibiotic Resistance Prevention And Control (ARPAC) project organized by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), continue to survey the antibiotic usage. Table 1 and 2 provide an extract from antibiotic use in several hospitals.

In general, antibiotic consumption in Bulgaria remains high, and is characterized by an increase in the usage of third generation cephalosporins and fluoroquinolones, the antimicrobial agents contributing most to the selection of resistant strains.

Antibiotic Stewardship

Bulgaria was one of the first countries to develop a National antibiotic policy. In 1999 an expert committee, along with the Ministry of Health (majority of the representatives from APUA), started the Program for Antimicrobial Resistance Surveillance and Rational Antibiotic policy, approved by the MH in 2001. The change of government, however, delayed the immediate introduction of this program: several years later it has been executed only in part, due to the lack of financial support.

Today, a hospital's antibiotic policies form an integral element of its accreditation of hospitals. Clinical microbiologists, as leaders of a multidisciplinary antibiotic team, are charged with responsibility of the program. Each hospital has a list of essential antibiotics. In general, the policy is restrictive. In the Medical Institute, Ministry of the Interior, there are three levels of antibiotic prescribing, instituted after discussion with all clinicians. Each clinical department elaborates its own clinical guidelines for the use of antibiotics. Several audits of antibiotic prescriptions have been conducted, which has contributed to the amelioration of antibiotic usage. Annual Reports from the Clinical Microbiology laboratory about ARS and antibiotic consumption are being presented and discussed at hospital Medical Council. Despite these activities, and every-day consultations, the results are suboptimal. One reason is the epidemiologic situation in the country. Furthermore, rational antibiotic therapy necessitates the optimal dosage regimen of the most effective antibiotic, and not giving preference to cheaper one. Keep in mind that Bulgaria is one of the countries with the lowest GDP in Europe, and as such the funds for health-care are smaller. Another, not completely achieved aim is the very early start of appropriate therapy for severe systemic infections.

In practice, antibiotic stewardship is not easily achieved. It requires stricter infection control, improved regulation, increased investment, and support from the government and international organizations.

Table 2. Antibiotic usage in 2011 in Pediatric University Hospital, Sofia, Bulgaria [4]

Antibiotics	DDD/100 bed-day	Antibiotics	DDD/100 bed-day
Fluoroquinolones	5.3	Carbapenems	0.5
Tetracyclines	0.2	Cephalosporins	21.2
MLS	6.3	1st generation	10.8
Macrolides	5.8	2nd generation	0.2
Lincosamides	0.5	3rd generation	10.0
Co-trimoxazole	0.8	4th generation	0.2
Penicillins	8.5	Aminoglycosides	2.9
with extended spectrum	2	Imidazoles	4.1
with anti-pseudomonas activity and β-lactamase inhibitor	6		

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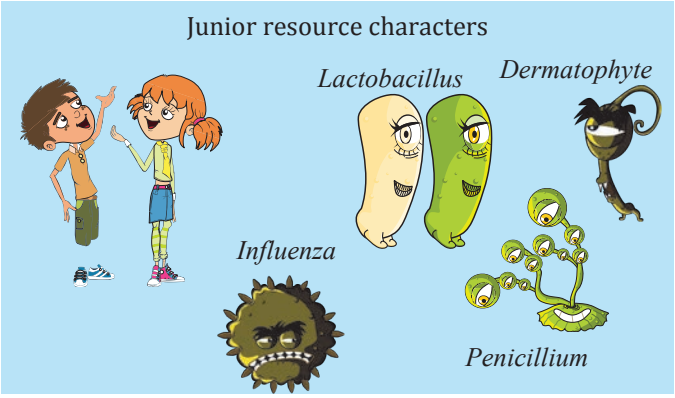
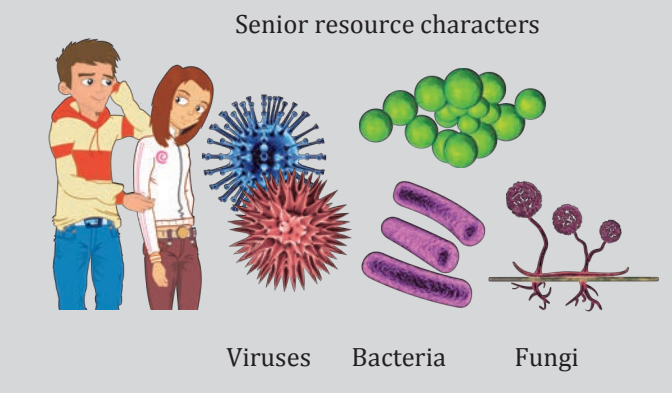
APUA Chapter Reports





APUA-UK Update

Dr. Cliodna McNulty, President of APUA-United Kingdom and her team have developed the

'e-Bug' Website, a European wide antibiotic and hygiene teaching resource for junior and senior school children. The project not only reinforces an awareness of the benefits of antibiotics, but also teaches prudent antibiotic use, and how inappropriate use can have an adverse effect on an individual's good microbes and antibiotic resistance in the community. An article published in Microbiology Today provides details on the development of this website and the resources it provides.

For 2012 the team have developed seven new online games for students (see below) and two lesson plans for teachers covering farm hygiene (junior schools) and chlamydia (senior schools).

The e-Bug partnership consists of 24 countries providing united health messages, with the resources being translated into all EU languages and also Turkish. In the 2011-2012 academic year there have been over 58,000 hits to the English website alone from 177 different countries and territories. The website also receives a large number of hits from non partner countries, for example, the Portuguese website has had as many hits from Brazil as Portugal.

Lecky DM, Hawking MKD, McNulty CAM. e-Bug – Making Microbiology and Hygiene Child's Play. Microbiology Today. **2011** May: 112-7.

APUA-Nepal Update

APUA-Nepal will be making two presentations at the First International Conference on Infectious diseases and Nanomedicine 2012 scheduled for December 15-18, 2012 in Kathmandu, Nepal. The topics of the presentation are "Common Isolates and their Antibiogram in T.U Teaching Hospital (TUTH), a tertiary care hospital in Nepal" and "Efforts of APUA-Nepal in Reducing the Emergence and Spread of Resistance."

APUA-Australia

APUA-Australia will be hosting its annual meeting "Antimicrobials 2013" from February 21 to 23, 2013 in Sydney, Australia. Dr. Peter Davey, University of

New Games in 2012

Soapy Soakers: Be a microbe buster on the skin! (Hand hygiene)
Bogey Bus: What's the best way to stop germs spreading in a sneeze (Respiratory Hygiene)
Chicken Surprise: How safe is the food you cook? (Food Hygiene)
Doctor Doctor!: Can you treat the patient before the time runs out! (AMR)
Mixed-up Microbes: There are three types of microbes, but do you know which is which?
Happy Holidays: Get your holiday vaccine before the holiday viruses get you (Vaccinations)
Body Busters: Kill the body bugs before they get you. Remember – antibiotics don't kill viruses!

Dundee in Scotland will be presenting the plenary "Antimicrobials Stewardship", and Drs. Louis Rice, Brown University and Fred Tenover, Cepheid in the USA will be presenting "Rapid Diagnostics and Appropriate Antibiotic Use" and "Molecular Diagnostics for Infectious Diseases: From DNA Probes to Whole Genome Sequencing, An Insider's Perspective" respectively. Dr. Matthew Cooper from the University of Queensland will be presenting the plenary "New Antimicrobial Discovery: Promise versus Reality?"

APUA-Georgia Update

APUA-Georgia was established in 2003 and managed by Professor Alexander Nanuashvili until his death in October 2011. His wife, Dr. Tamar Davitashvili has since assumed leadership of the chapter.

In 2009, Prof. A. Nanuashvili published the volume "Bacterial Infections", which has been of paramount importance for Georgian physicians and microbiologists.

Through 2010-2011, before his severe illness, Prof. Nanuashvili conducted many seminars for Georgian doctors in the field of prudent use of antibiotics. In 2010, Prof. Nanuashvili headed the creation of the country's monitoring system and associated data bases of antimicrobial resistance. In the same year, APUA-Georgia conducted a national conference on antibiotic resistance in order to review the data gathered for the antibiotic resistance monitoring system.

Prof. Nanuashvili's final work "Antimicrobial Agents", will shortly be published in the form of a periodical newsletter for circulation among doctors. Since 2011, APUA- Georgia has been taking part in the Study for Monitoring Antimicrobial Resistance Trends (SMART) being conducted by the International Health Management Associates, Inc (IHMA) to monitor worldwide antimicrobial resistance trends among aerobic and facultatively anaerobic Gram-negative bacilli (GNB) isolated from intra-abdominal infections.

In 2012, APUA-Georgia has been conducting seminars for doctors on topics related to antibacterial therapy. Soon, they plan to analyze the data collected by the national resistance monitoring system.

Attendees of the Symposium held for establishment of APUA-Mayabeque sub-chapter. APUA-Cuba has created sub-chapters in 9 out of Cuba's 16 provinces.

APUA-Cuba Update

APUA-Cuba continues to grow, with more than 1,400 members in over 60 medical specialties. Dr. Moisés Morejón (Manual Fajardo Hospital) and his colleagues have held multiple symposia on antimicrobial resistance and the need for new antibiotics. One of its recent conferences discussed the applicability of modern diagnostic technology in detecting HAI pathogens and identifying resistant phenotypes in immunocompromised patients.

APUA-Cuba has proposed national guidelines, citing APUA recommendations for correct antibiotic use in critical-care patients in the face of rising rates of HAIs and infection from multidrug-resistant *Acinetobacter baumannii*. Other proposed guidelines include those for antibiotic use in surgical prophylaxis, and parameters for sequential antibiotic therapies that will hopefully evolve into sophisticated antibiotic stewardship programs.

Pneumonia is another growing concern in Cuba, especially in children, and has stimulated discussions on the importance of correct diagnosis and provided an incentive for pneumococcal vaccine development. APUA -Cuba has evaluated international guidelines for community-acquired pneumonia, citing guidelines from IDSA/ATS and the South American working groups ConsenSur and SEPAR as being the most useful.

This year Dr. Morejón published *Enfermedades Tropicales Mayores: Enfermedades Olvidadas o Desatendidas* (Forgotten & Neglected Tropical Diseases).

APUA Leadership Award 2012

Professor Roman S. Kozlov, M.D., M. Sc., D.Sc. And APUA-Russia

The Alliance for the Prudent Use of Antibiotics (APUA) is pleased to present the 2012 APUA Leadership Award to Professor Roman S. Kozlov and APUA-Russia for sustained leadership to contain antibiotic resistance in Russia and the adjacent region. This award also recognizes the Chapter's collaborative efforts with the Inter-Regional Association for Clinical Microbiology & Antimicrobial Chemotherapy (IACMAC) and the Institute of Antimicrobial Chemotherapy (IAC) of Smolensk State Medical Academy (SSMA).

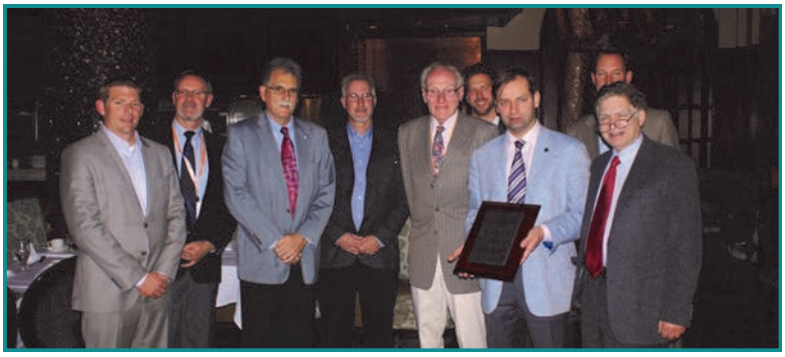
As President of APUA-Russia, Professor Kozlov has led the remarkable efforts of this chapter to promote the prudent use of antibiotics. APUA-Russia has been extensively involved in activities throughout Russia, Belarus, Ukraine, and other countries of the Former Soviet Union for the establishment of a network of sentinel laboratories and organization of continuous surveillance programs of both community and hospital-acquired pathogens. APUA-Russia is based at SSMA in Smolensk, where Professor Kozlov serves as IAC Director. Collaboration with the IAC has provided the laboratory facilities to develop the surveillance work. The results of these studies have been used as a basis for development of national guidelines on the management of community-acquired pneumonia, hospital-acquired pneumonia, intra-abdominal infections, and skin and soft-tissue infections.

This year, the APUA Leadership Award recruited nominations for an outstanding young professional who has demonstrated extraordinary leadership. Professor Kozlov was recommended for this award by Dr. Stephen A. Lerner of Wayne State University and a member of APUA's Scientific Advisory Board. Professor Kozlov assumed leadership of the APUA-Russia chapter at a young age and has successfully brought to fruition many of the goals first envisioned by his mentor and predecessor, Dr. Leonid Stratchounski. In his letter of nomination, Dr. Lerner indicates,

> "This award and these accomplishments stand on the vision of Dr. Leonid Stratchounski whose untimely death in June 2005 was a grave tragedy for the world's interests in antibiotics and resistance. Fortunately, part of Dr. Stratchounski's vision was to identify promising young people in Smolensk and to groom them for excellence in the field of antibiotics. The prime example is Dr. Roman Kozlov. Dr. Kozlov became Dr. Stratchounski's lieutenant, and he was successfully able to assume the leadership positions he holds today."

Professor Kozlov also serves as President of IACMAC, an organization that has been a beacon for epidemiologic, clinical and basic research on antibiotics and their appropriate usage. The efforts of IACMAC to communicate their research to scientists and practitioners across the expanse of the Former Soviet Union has a provided a great service to the field of infectious disease. Notably, IACMAC has developed an interactive 'Map of Antimicrobial Resistance of Russia' available freely on the web site www.antibiotic.ru for the use of physicians and microbiologists throughout the world. Furthermore, IACMAC has organized an exemplary distant education course on antimicrobial therapy which has been successfully completed by more than 600 physicians.

APUA is pleased to recognize Professor Kozlov's leadership and his success in influencing the prudent use of antibiotics in Russia and the region. In offering his congratulations Dr. Stuart B. Levy, President of APUA stated, "Roman Kozlov represents a class of emerging young leaders whose dedication is essential to ensure antibiotic effectiveness. His leadership demonstrates the value of the APUA global network and its affiliated chapters in 66 countries throughout the world."



While APUA's traditional ICAAC reception was not held this year, the award was presented to Professor Kozlov at a special Leadership Award dinner at ICAAC co-hosted by Drs. Thomas F. O'Brien and Stephen A. Lerner of APUA. The dinner was attended by representatives from some of corporate sponsors. We plan the traditional APUA reception at next year's ICAAC in Denver, Colorado and will be formally recognizing Professor Kozlov and APUA-Russia then.

For a list of previous award winners, please see the APUA website.

APUA-Russia is organizing the II Volga Region Conference on Antimicrobial Therapy in Samara, Russia from October 11-12, 2012. The program in English can be viewed here.

APUA Headquarters in Action

New APUA report: Expert advice for antibiotic stewardship programs

APUA surveyed members from the APUA Scientific Advisory Board regarding strategies for effective implementation of antibiotic stewardship programs (ASP) in healthcare facilities. They pointed out both technical and perceptual challenges to successful implementation of ASPs and some ways to overcome these obstacles. Contributing experts were:

- Thomas F. O'Brien, M.D. (Brigham and Women's Hospital)
- Shira I. Doron, M.D. (Tufts Medical Center)
- Philip D. Walson, M.D. (Geörg-August-Universität School of Medicine; Clinical Therapeutics)
- Alfred DeMaria, Jr., M.D. (Massachusetts Department of Public Health)

Read the results of this survey on the APUA website. More information on this topic is available in the following past APUA Newsletters:

- Enhancing Infection Control with Antibiotic Stewardship (Vol.29 No.3)
- Antibiotic Stewardship Gaining Traction: Recommended Models and Resources (Vol.29 No.1)
- Antibiotic Stewardship Programs: Proven Strategies to Preserve Medicine's "Magic Bullets" (Vol.24 No.1)

Additional resources are found on our website under For Practitioners: Treatment Guidelines and Stewardship

APUA signs letter to the US Congress requesting $547 million for BARDA

The letter is addressed to the House and Senate Appropriations Committees and asks for an appropriation of at least $547 million for Fiscal Year 2013 for the Biomedical Advanced Research and Development Authority (BARDA) . BARDA is intended to provide "an integrated, systematic approach to the advanced development and purchase of necessary medical countermeasures (MCMs), including vaccines, biological and small molecule therapeutics, antiviral drugs, antifungal drugs, and antibiotics, diagnostics, respiratory devices, and other medical supplies." Although the program has been underfunded since its inception, investments by BARDA have resulted in the development of new therapeutics such as a new smallpox antiviral and vaccine for HIV patients, anthrax treatments as well as progress toward developing new anthrax recombinant vaccines. Since private investment in antibiotic research and development has plummeted, BARDA has become an important source of funding for research and development of novel antibiotics for treatment of multi-drug resistant pathogens.

APUA Leadership Statement advocates strengthening FDA Draft Guidance on antibiotic use in livestock

The FDA Draft Guidance #213 ("Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with Guidance for Industry #209") asks drug companies to voluntarily remove "growth promotion" from the lists of FDA-approved uses on their products' labels and instead list disease treatment, control, or prevention. This guidance was open for public comment until July 12, 2012.

APUA, in partnership with PEW Charitable Trusts has been advocating for stricter drafting and enforcement of this guidance. APUA commented on the guidance in the form of an organizational letter urging the FDA to make this change in labeling practices an enforceable rule rather than a recommendation. The letter also encouraged the FDA to remove "disease prevention" from the list of approved uses, because allowing it can, in practice, be identical to allowing the use of antibiotics for "growth promotion".

In addition, APUA developed a leadership statement addressed to President Obama and FDA Commissioner Hamburg. APUA reached out to colleagues for support and this statement was signed by 21 leaders in science and medicine including 4 Nobel Laureates and 5 ASM Presidents. Please see statement on the following page.

APUA
ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS

July 10, 2012

President Barack Obama
1600 Pennsylvania Ave. NW
Washington, DC 20500

and

The Honorable Margaret Hamburg, MD
Commissioner, Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear President Obama and Commissioner Hamburg:

As recognized leaders in the U.S. scientific and medical community, we applaud the FDA's recent actions to promote judicious use of antibiotics in food-producing animals through recommendations, delineated in its guidance documents. We support your guidance that antibiotics not be used for growth promotion and feed efficiency, and that there be veterinary oversight in the dispensing of antibiotics—particularly in feed and water, where whole herds and flocks are the recipients. These voluntary guidances represent a significant shift in U.S. public health protection, as they begin to address the high risks that non-judicious use of antimicrobials in animals pose for human health – in the form of increases in drug resistance and potential treatment failures. We are concerned, however, that they are insufficient and that stronger regulation is needed.

There is no reason to expect compliance from agribusiness, in view of its long history of rebuffing regulatory efforts to curb antibiotic use. In addition, FDA considers use of antibiotics for disease prevention to be a therapeutic use, essential to animal health. Since many drugs that have been approved for growth promotion purposes have also been approved for routine disease prevention, we are concerned that industry will not reduce overall antibiotic use, but merely shift from growth promotion to prevention. We request that FDA address antibiotics used for prevention and recommend and provide incentives for using alternative strategies, such as vaccines, probiotics, and improved management practices, for disease prevention and control. We suggest that further guidance clearly describe plans for monitoring progress. Specifically, the further development of our national antimicrobial resistance monitoring system to include more geographic representation and species-specific data on resistance and antimicrobial use in animals and humans would go a long way to inform and evaluate practitioner compliance and outcomes.

According to the U.S. CDC and WHO, antimicrobial resistance is one of the top five public health threats. What is needed is an overall reduction in antimicrobial use, achieved by offering economic incentives to adopting alternatives in conjunction with further regulatory and legislative action. We strongly support the passage of the Preservation of Antibiotics for Medical Treatment Act (PAMTA, H.R. 1549, S.619), which would withdraw the use of seven classes of antibiotics that are critically important to human health from food animal production, unless specific disease conditions apply. Now is the time to act. Thank you for your consideration.

Sincerely yours,

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AAAS** President
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Julian Davies, PhD
ASM Past President
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ASM Past President
Thomas Schmidt, PhD
2011 President Elect ASM
Alexander Tomasz, PhD
Professor, Head of Rockefeller Laboratory

News and Publications of Note

HIVMA and IDSA Update Policy Recommendations for HIV

In conjunction with the July 2012 International AIDS Conference, the Infectious Disease Society of America's (IDSA) Center for Global Health Policy and HIV Medicine Association (HIVMA) featured the 2012 HIV compendium, *Clinical Issues in HIV Medicine*, and updated policy recommendations (PDF) following the HPTN 052 study, the first large-scale, randomized controlled trial showing that antiretroviral therapy reduces the risk of sexual transmission of HIV to an uninfected partner.

IDSA Updates Group A Strep Treatment

An update to the 2002 clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis was made by the Infectious Diseases Society of America in September 2012 (see *Clinical Infectious Diseases*).

In order to deter inappropriate use of antibiotics, the guideline advises that once a strep infection is confirmed by testing, penicillin or amoxicillin, not cephalosporin should be used as first-line therapy. The IDSA also recommends that children who suffer recurrent strep throat should not have their tonsils surgically removed solely to reduce the frequency of infection.

A podcast with the lead author has been developed and other tools, such as mobile device and pocket-card formats for use at the point of care, are in development (see IDSA: practice guidelines section).

CDC Updates STD Guidelines

According to the new guidelines published in the Center of Disease Control and Prevention's *Morbidity and Mortality Weekly Report* in August 2012, oral cephalosporins are no longer recommended for gonorrhea treatment. The rationale for this change is provided by recent data from CDC's Gonococcal Isolate Surveillance Project that demonstrate a significant increase (17-fold from 2006 to 2011) in the percentage of *Neisseria gonorrhoeae* isolates showing tendency for cefixime resistance. CDC recommends that doctors immediately stop routine use of cefixime. In order to preserve the last remaining antibiotic considered highly effective for gonorrhea treatment, combination therapy with intramuscular ceftriaxone, plus either oral azithromycin or doxycycline, is now recommended for uncomplicated cases. If ceftriaxone is not used due to complications, a test of cure is recommended one week after treatment.

Since cefixime and ceftriaxone are in the same class of antibiotics, it is only a matter of time before the fast-mutating *N. gonorrhoeae* develop resistance to cephalosporin as well. Although there are no documented treatment failures in the United States, untreatable gonorrhea has already been reported in Asia and Europe. In case of treatment failure under current guidelines, the CDC should be notified within 24 hours. A specimen should be collected for culture and sensitivity, and the patient should be re-treated. The patient's recent partners should also be treated.

Tufts Studies Novel Storage Medium for Antibiotics and Vaccines

Conventional methods of antibiotic and vaccine storage depend on refrigeration to maintain their potency. In resource-poor settings, however, cold storage is not always available. For example, after six months at 25°C, conventionally freeze-dried MMR (measles, mumps, rubella) vaccine retains only 60-75% of its potency, and becomes virtually useless at 45° C.

Dr. David Kaplan and his team have described a new technique for packing antibiotics and vaccines (July issue of the *Proceedings of the National Academy of Sciences*) that involves boiling silk cocoons in sodium carbonate to extract silk fibroin. The fibroin is then treated with salt and preservative and spread out into sheets and freeze-dried. With this new silk sheet packing, the MMR vaccine retains about 85% of it's potency after six

months, regardless of temperature. Similar results were seen with tetracycline, and penicillin. Vaccines and antibiotics stored in this silk fibroin matrix are yet to be tested in humans, but the risk of adverse effects is minimal given that silk, often used in sutures, is harmless to people.

CDDEP's Visualization Series Focuses on Two Antibiotic Resistance Topics

The Center for Disease Dynamics, Economics and Policy website hosts a visualization series that examines correlations between outpatient prescribing rates of oral vancomycin and *C. difficile* mortality in the United States. The strength of the relationship suggests that drug utilization data can be a cost-effective tool for disease surveillance.

Another item in this visualization series focuses on the alarming increase in retail sales of carbapenem antibiotics in India and Pakistan. Without the enforcement of strict regulation curbing over the counter sales, there is a grave risk that resistant organisms will emerge and become almost impossible to treat.

New UN Reports highlight progress on child survival

The UN Inter-agency Group for Child Mortality Estimation (UN-IGME) has released new data showing that the reduction in the pace of child deaths has accelerated sharply since 2000. Similar trends are noted in the UNICEF's Report: Committing to Child Survival: A Promise Renewed – Progress Report 2012, which summarizes mortality estimates along with the top killers of children under five, and outlines the practical strategies that are needed to accelerate progress. Indeed, progress has been made over the last two decades—-thanks to sound strategies, adequate resources and, above all, political will.

Bringing diagnostics to resource-poor settings

Utilizing a fictitious but dramatic case-in-point example, Michael Ingerson-Mahar brings to life the dire scenarios of real-life people whose lack of access to point-of-care diagnostic tests (POCTs) in the developing world can mean the difference between life and death (Microbe, Sept 2012). In Sept 2011, the American Academy of Microbiology (AAM) convened a panel of microbiologists, engineers, epidemiologists and public health officials to consider questions surrounding the myriad, complex steps involved in the design and development of POCTs. Their report, "Bringing the Lab to the Patient: Developing Point-of-Care Diagnostics for Resource Limited Settings" discusses the impacts that POCTs could have on clinical decision-making and highlights the need for interactive discourse between the many players who must collaborate effectively to bring promising POCTs to remote areas. Many obstacles must be surmounted to achieve the ideal qualities of a POCT for these sites: i.e., affordable, sensitive, specific, user-friendly, robust and rapid (ASSURED), as well as integration into the larger health care system. Matching the needs of decision-makers at resource poor locations with the new technologies that are emanating from the research community is a current challenge. Deficits in communications channels that exist between the two, coupled with regulation and licensing issues, present enormous hurdles to overcome. Efforts spearheaded by the journal Lab on a Chip and the Foundation for Innovative New Diagnostics (FIND), for example, are making progress towards filling these gaps.

CDC Funds Help Prevent HAIs

The Affordable Care Act has allowed funding of infrastructure to implement state-based health care-associated infection (HAI) prevention programs. Sixteen states are receiving funds for building multi-facility prevention initiatives. Previous investments have resulted in saved lives and health care costs in 21 states, demonstrating significant reductions in HAIs. Four states will receive funding for advancing the national implementation of electronic laboratory records. The funds will improve capacity to receive, validate, process, and use incoming electronic laboratory records messages in surveillance systems and ensure timely reporting of health care-associated infections to CDC's National Healthcare Safety Network.

Upcoming Events

September 29- October 4, 2012: ASM's 6th Conference on Biofilms in Miami, FL.

October 11-12, 2012: The Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy's II Volga Region Conference on Antimicrobial Therapyin Samara, Russia.

October 17-21, 2012: IDSA's inaugural **ID**Week will be held in San Diego, CA. IDWeek is the first-ever combined meeting of the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiologyof America (SHEA), the HIV Medicine Association (HIVMA), and the Pediatric Infectious Diseases Society (PIDS). The theme of this year's meeting is "Advancing Science, Improving Care" and will feature the latest science and bench-to-bedside approaches in prevention, diagnosis, treatment, and epidemiology of infectious diseases, including HIV, across the lifespan.

October 22-26, 2012: ASM's 4th Conference on Beneficial Microbes in San Antonio, TX.

October 27-31, 2012: APHA's 140th Annual Meeting and Expo will be held in San Francisco, CA on the topic of "Prevention and Wellness Across the Life Span." The APHA meeting attracts more than 13,000 national and international physicians, administrators, nurses, educators, researchers, epidemiologists, and related health specialists to address current and emerging issues in health science, policy, and practice.

November 12-18, 2012: CDC's Get Smart About Antibiotics Week.

November 27-28, 2012: World Animal Health Congeress in Kansas City, MO.

February 4-8, 2013: Tufts CSDD "Postgraduate Course in Clinical Pharmacology, Drug Development and Regulation" in Boston, MA.

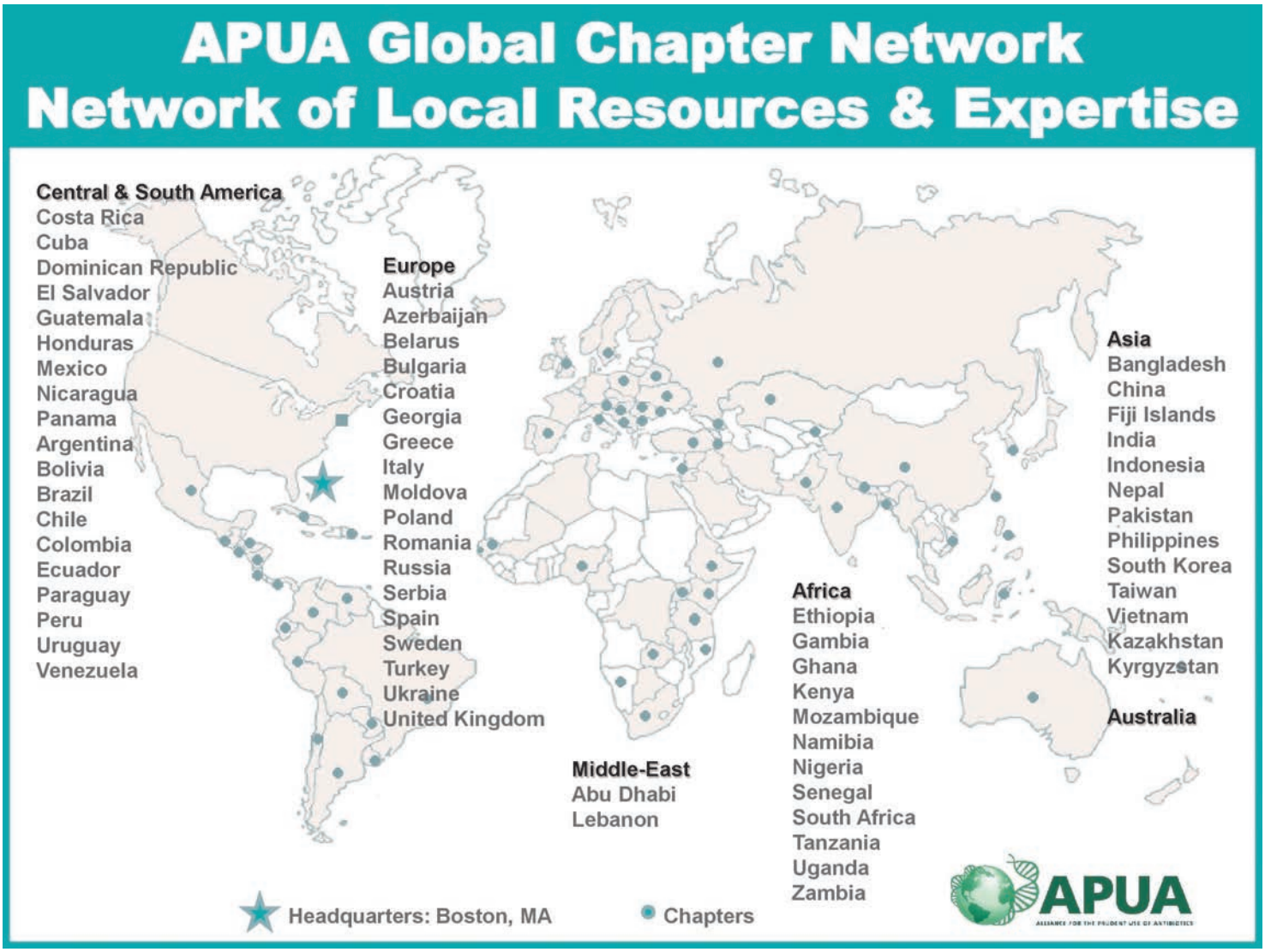
February 21-23, 2013: Australian Society for Antimicrobial's Annual meeting "Antimicrobials 2013" in Sydney, Australia.

March 14, 2013: British Soceity for Antimicrobial Chemotherapy's Spring Meeting 2013 in London, UK.

About Us

Antibiotics are humanity's key defense against disease-causing microbes. The growing prevalence of antibiotic resistance threatens a future where these drugs can no longer cure infections and killer epidemics run rampant. The Alliance for the Prudent Use of Antibiotics (APUA) has been the leading global non-governmental organization fighting to preserve the effectiveness of antimicrobial drugs since 1981. With affiliated chapters in more than 66 countries, including 33 in the developing world, we conduct research, education and advocacy programs to control antibiotic resistance and ensure access to effective antibiotics for current and future generations.

Our global network of infectious disease experts supports country-based activities to control and monitor antibiotic resistance tailored to local needs and customs. The APUA network facilitates the exchange of objective, up-to-date scientific and clinical information among scientists, health care providers, consumers and policy makers worldwide.



APUA

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