### FEATURE ARTICLES

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Introduction to this issue</td>
<td>Bonnie Marshall (APUA Staff)</td>
</tr>
<tr>
<td>4</td>
<td>Antibiotics in aquaculture: impacts and alternatives</td>
<td>Mario Caruffo DVM and Paola Navarrete PhD, Assistant Professor, University of Chile, Santiago, Chile</td>
</tr>
<tr>
<td>8</td>
<td>Update: Nebulized antimicrobial drug delivery</td>
<td>Philip D. Walson, Visiting Professor, Department of Clinical Pharmacology, University Medical Center, Goettingen, Germany</td>
</tr>
</tbody>
</table>

### APUA HEADQUARTERS, CHAPTER & RESISTANCE NEWS

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>APUA Headquarters in Action</td>
</tr>
<tr>
<td>11</td>
<td>International Chapter Updates</td>
</tr>
<tr>
<td></td>
<td>- Chapter Spotlight: APUA-Bulgaria</td>
</tr>
<tr>
<td></td>
<td>- APUA-South Africa</td>
</tr>
<tr>
<td>14</td>
<td>Resistance in the News</td>
</tr>
<tr>
<td>17</td>
<td>Upcoming Events</td>
</tr>
<tr>
<td>18</td>
<td>Publications of Interest</td>
</tr>
<tr>
<td>20</td>
<td>About Us</td>
</tr>
</tbody>
</table>

In a study of 6 farmed seafood types appearing in U.S. markets and originating from 11 different countries, scientists from Arizona State University have discovered traces of 5 antibiotics, including oxytetracycline, 4-epi oxytetracycline, sulfadimethoxine, ormetoprim and virginiamycin. While still compliant with FDA regulations, these low-levels of antibiotic create concern over long-term resistance development. Read more about the impacts of antibiotics on fish microbiota and alternatives to their use in this issue’s article by Caruffo and Navarrete.
Chief Executives
Stuart B. Levy, President
Thomas F. O’Brien, Vice President

Board of Directors
Stuart B. Levy, Chairman
Sherwood Gorbach
Bonnie Marshall
Thomas F. O’Brien
Arnold G. Reinhold
Dennis Signorovitch
Philip D. Walson
Mary Wilson

APUA Staff
Barbara Lapinskas, Administrative Director
Jane Kramer, Program Director
Kathleen Young, Projects Consultant
Stuart B. Levy, Newsletter Editor
Bonnie Marshall, Associate Editor
Casi Kadangs, Assistant Editor

Advisory Board (cont)
Jacobo Kuperstoch, USA
Jay A. Levy, USA
Scott McEwen, Canada
Jos. W.M. van der Meer, The Netherlands
Richard P. Novick, USA
Iruka Okeke, USA & Nigeria
Maria Eugenia Pinto, Chile
Vidal Rodriguez-Lemoine, Venezuela
José Ignacio Santos, Mexico
Mervyn Shapiro, Israel
K. B. Sharma, India
Atef M. Shibli, Saudi Arabia
E. John Threlfall, United Kingdom
Alexander Tomasz, USA
Thelma e. Tupasi, Philippines
Anne K. Vidaver, USA
Fu Wang, China
Thomas E. Wellems, USA
Bernd Wiedemann, Germany

APUA Project Partnerships:
The Bill and Melinda Gates Foundation
The Pew Charitable Trusts
U.S. National Institute of Health (NIH)
Pan American Health Organization (PAHO)
U.S. Agency for International Development (USAID)
U.S. Department of Agriculture
U.S. Office of Homeland Security
National Biodefense Analysis and Countermeasures Center
The World Bank
World Health Organization (WHO)
Centers for Disease Control and Prevention (CDC)
U.S. Food and Drug Administration
Ministries of Health
U.S. Defense Threat Reduction Agency

Supporting Chapters:
APUA—Abu Dhabi
APUA—South Korea
Australian Society for Antimicrobials (APUA-Australia)
British Society for Antimicrobial Chemotherapy (APUA-UK)

APUA gratefully acknowledges unrestrict-ed grants from corporate sponsors:

Disclaimer
APUA accepts no legal responsibility for the content of any submitted articles, nor for the violation of any copyright laws by any person contributing to this newsletter. The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by APUA in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The APUA Newsletter (ISSN 1524-1424) © 2015 APUA
Since 1983, the APUA Newsletter has been a continuous source of non-commercial information disseminated without charge to healthcare practitioners, researchers, and policy-makers worldwide. The Newsletter carries up-to-date scientific and clinical information on prudent antibiotic use, antibiotic access and effectiveness, and management of antibiotic resistance. The publication is translated into three languages and distributed to over 7,000 affiliated individuals in more than 100 countries. The material provided by APUA is designed for educational purposes only and should not be used or taken as medical advice. We encourage distribution with appropriate attribution to APUA. See previous editions of the Newsletter on the APUA website.

*APUA welcomes letters to the Editor. Please send us your thoughts and questions. Names will be published but not addresses. All letters may be edited for style and length.

Phone: 617-636-0966 | Email: apua@tufts.edu | Website: www.apua.org
This issue of the APUA Newsletter touches on two diverse topics related to antibiotic use, both environmentally and clinically. The topic of antibiotics and their impacts on the aquaculture industry is addressed by Caruffo and Navarrete. This issue has long festered in the shadows cast by the enormous focus placed on antibiotic growth promotion use in food animal farms. The burgeoning fish farming industry—the fastest growing form of food production in the world—has tripled in the previous two decades. Asia accounts for 89% of production, with China as the largest producer. Up to 90% of fish consumed in the U.S. is imported, and half of that is farm-raised. With its frequently unregulated and questionable antimicrobial use practices, the industry bears closer scrutiny as a potential contributor to the escalating antibiotic resistance problem.

Our second article discusses the status and future of aerosolized antibiotics—a method of delivery that was first explored in the 1950’s. Early attempts at aerosolization, using penicillin G, ticarcillin, ceftazidine and carbenicillin, were largely abandoned due to the severe side effect of bronchospasm and other poor outcomes that may have been due to shortcomings in methodology. The rise of ventilator-associated pneumonia (pneumonia in a patient who has been mechanically ventilated for at least 48h) due to multidrug resistant pathogens such as Acinetobacter baumannii and Pseudomonas aeruginosa and the need for targeted antimicrobial therapy have prompted a reexamination of this method for antibiotic delivery. Today - both jet and ultrasonic nebulizers effectively deliver therapeutic levels of drug in >90% of patients with minimal systemic dispersion. The article by Walson discusses current practices and the continuing need for clinical trials to resolve some ongoing issues with the use of this mode of therapy.
Antibiotics in aquaculture: impacts and alternatives

Mario Caruffo, DVM and Paola Navarrete, PhD, Assistant Professor, Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile

The aquaculture industry provides high quality protein for billions of people, with fish representing 20 percent of the daily animal protein intake for about 3 billion.1 As a significant percentage of wild fish stocks are experiencing depletion, nearly 50 percent of the world’s fish supply now derives from aquaculture.2 Antibiotics in aquaculture have been used primarily as therapeutic and prophylactic agents, with varying regulations depending on the country, which complicates the determination of the actual quantities used. Some data show large variations between countries, with use ranging from an estimated 1 g per metric ton of production in Norway to 700 g per metric ton in Vietnam.3 Chile is the second largest salmon producer following Norway, however, its antibiotic use is 60 times greater than the other three top salmon-producing countries combined (Norway, Scotland and British Columbia).4,5

Antibiotics are primarily administered to fish via their food. Of this, an estimated 30% of total antibiotic, and 80% of the ingested, antibiotic-mediated feed reach the environment through unconsumed and unabsorbed food, respectively.6 Antibiotics can remain active in water and sediments for long periods of time, depending on the concentration and type of the chemicals, with a large impact on biodiversity and selection of resistant bacteria.6 Studies examining the effect of antibiotics on the gut microbiota have shown similar impacts.

The gut microbiota of fish

The gut microbiota of fish have been extensively studied by culture and molecular techniques.7-12 While bacterial concentrations are lower and diversity is less broad than in the mammalian intestinal microbiota, the gut microbiota of fish simulate important evolutionarily conserved responses in the host.13 The main bacterial phyla found in the fish gut are Proteobacteria, Firmicutes, Bacteroidetes, Fusobacteria, Actinobacteria, Clostridia, Bacilli, and Verrucomicrobia. Studies in germ-free fish have revealed the roles of this microbiota, which include epithelial proliferation, the promotion of nutrient metabolism, and innate immune responses.13-15 Composition of the microbiota, in terms of the type of bacteria present in the digestive tract, determines the host responses.13 Consequently, the eventual modification of the microbial composition by antibiotic treatment could lead to alteration in host response.

Antibiotic effects on host microbiota

Studies on the impacts of antibiotics on the gut microbiota in mammals have revealed not only modifications in bacterial load and composition,16 but also an increase in the risk or incidence of some diseases.17-23 Antibiotics generate similar changes in fish as well. The impacts of antibiotic on bacterial load differ, depending on the antibiotic type and its concentration, as well as the fish species involved. Oxolinic acid (OA), oxytetracycline (OTC) and sulphafurazole reportedly cause an increase in bacterial densities throughout the digestive tract of rainbow trout (Salmo gairdneri Richardson).24 In contrast, erythromycin and penicillin G both produced a rapid reduction of bacterial counts,24 as did three dosages of OA (6, 12, and 24 mg/kg over 7 days).25 The administration of OTC (3g/kg in diet over 3 weeks) to Atlantic salmon (Salmo salar L.) reduced significantly the total viable gut population.26 This reduction was greater in bacteria from digesta when compared to those associated with the mucosa—with
In our study, OTC (75 mg/kg for 10 days) did not affect the bacterial load of cultivable bacteria. The antibiotic growth promoters flavomycin (20 mg/kg) and florfenicol (20 mg/kg), and the combination of two (10+10 mg/kg), dramatically reduced the total intestinal counts in hybrid tilapia. Studies show that antibiotics can also alter the composition of the gut microbiota of fish, triggering a reduction in bacterial diversity and enabling the proliferation of opportunistic or resistant bacteria. The administration of three dosages of OA (6, 12, and 24 mg/kg over 7 days) in rainbow trout showed that intestinal Aeromonas remained susceptible to OA. In contrast, OA stimulated the proliferation of OA-resistant Aeromonas in output water. The authors suggest that the selection and emergence of this resistant bacteria occurred following the excretion of the feces, rather than within the fish intestines themselves.

We have examined the effect of OTC (75 mg/kg) administered through feed for 10 days on the diversity of the cultivable bacteria from the intestines of healthy juvenile Atlantic salmon (Salmo salar). While the intestinal microbiota of untreated fish remained diverse (predominantly Pseudomonas, Acinetobacter, Bacillus, Flavobacterium, Psychrobacter, and Brevundimonas/Caulobacter/Mycoplana) diversity in the OTC-treated fish was markedly reduced and only the opportunistic pathogens Aeromonas veronii bv. sobria and A. salmonicida were isolated. Antibiotic treatment markedly increased the frequency of OTC-resistant bacteria from 0% pretreatment, to 60%, 33% and 25% on days 11, 21, and 28 post-treatment, respectively. The most frequent resistant determinants identified were tetE (78%) and tetD/H (22%).

Following 8 weeks of treatment with the growth promoters flavomycin (20 mg/kg) and florfenicol (20 mg/kg), and the combination of the two (10+10 mg/kg), bacterial diversity of the autochthonous intestinal microbiota of hybrid tilapia was affected as demonstrated by changes in band presence and intensity in DGGE gels. Alternatively, the oral administration of OTC (40 mg/kg) for 10 days to Solea senegalensis juveniles produced a significant reduction in bacterial richness, reflected by a reduced number of DGGE bands. The administration of this

<table>
<thead>
<tr>
<th>Antibiotic alternative</th>
<th>Advantages</th>
<th>Limitations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobial peptides</strong></td>
<td>Broad-spectrum activity</td>
<td>Susceptibility to protease degradation</td>
<td>31-35</td>
</tr>
<tr>
<td></td>
<td>Limited hemolytic and cytotoxic activity</td>
<td>Salt-dependent inactivation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proof-of-concept developed</td>
<td>Potential host toxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delivery and costs production</td>
<td></td>
</tr>
<tr>
<td><strong>Phage therapy</strong></td>
<td>Target specific</td>
<td>Potential for resistance development</td>
<td>36-38</td>
</tr>
<tr>
<td></td>
<td>Can synergize with antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixtures of multiple phages can be used to reduce resistance development</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-chain fatty acids</strong></td>
<td>Synergic effect with probiotics</td>
<td>High dose needed</td>
<td>39, 40</td>
</tr>
<tr>
<td></td>
<td>Can be delivered in feeds</td>
<td>Exact mode of action is unclear</td>
<td></td>
</tr>
<tr>
<td><strong>Bacteriocins</strong></td>
<td>Diverse repertoire</td>
<td>Potential for resistance development</td>
<td>41, 42</td>
</tr>
<tr>
<td></td>
<td>Target-specific</td>
<td>Susceptibility to protease degradation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can synergize with and reduce cytotoxicity of antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Probiotics, Prebiotics</strong></td>
<td>Maintain or improve commensal gut bacterial health</td>
<td>Mixed efficacy of single probiotics</td>
<td>43-46</td>
</tr>
<tr>
<td></td>
<td>Prevent pathogen colonization</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Improve host immunity or animal growth and production</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Essential oils (EOs)†</strong></td>
<td>Improve gut health</td>
<td>Exact mode of action is unclear</td>
<td>47, 48</td>
</tr>
<tr>
<td></td>
<td>Can be delivered in feeds</td>
<td>Effects are dependent on the concentration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can be used as preserving agents in sea food</td>
<td>and the EO combination used</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EO can be degraded in feed</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Alternatives to antibiotics in aquaculture: major advantages and limitations

† The most studied of the essential oils are thymol (thyme and oregano), cinnamaldehyde (cinnamon), anethole (anise), eugenol (clove), and carvacrol (oregano).
antibiotic was also linked to an up-regulation of genes related to apoptosis.\textsuperscript{29}

The general concerns about the effect of intensive antibiotic use also include ornamental fish. Recently, antibiotic resistance genes were detected in the microbiota of carriage water from ornamental fish,\textsuperscript{30} suggesting this ecological niche as a potential source of antibiotic resistance.

**Alternative treatments to antibiotics**

Antibiotic resistance among bacterial pathogens and concerns over the extensive use of antibiotics in animal production, including aquaculture, have gained global interest. This is reflected by tighter regulations on the prophylactic use of antibiotics and their presence as residues in aquaculture-derived products.

For a sustainable aquaculture industry, novel strategies to control bacterial infections are needed. Several alternatives to antibiotics have been developed for use in aquaculture. A brief summary of the currently available options, including their advantages and limitations, is described in Table 1. Some, such as probiotics, have been more intensively investigated, while other methods (e.g., antimicrobial peptides, bacteriocins, and phage therapy) are still in developmental phases, but hold a promising future. Although not all have been tested in aquaculture facilities, all are important prospects for developing new strategies that could be combined or used in rotation in order to maximize protection of animals, the environment, and public health, and to prevent further antibiotic resistance development.

**References**

2. FAO/WHO. The State of World Fisheries and Aquaculture.
Opportunities and challenges. (2014). Available at http://www.fao.org/3/d1ea9a1-5a71-4e42-86c0-f211107d1e16/i3720e.


Caruffo & Navarrete references continued on p. 13
Antimicrobial drugs are usually given by either oral or intravenous routes. Increasing interest has been shown in the inhaled route of administration using either drug powders or aerosols to treat a number of diseases including pneumonia and sinusitis, based on the possibility of achieving higher concentrations at the site of infection with less systemic drug exposure and less toxicity.¹

While antiviral and antifungal drugs,²-⁴ as well as other drugs (e.g., bronchodilators, diuretics, surfactants, prostanoids, and vasoconstrictors) are also being given by inhalation, most studies involve antibiotics, so this article will concentrate on inhalation administration of antibiotics, especially given as aerosols rather than by use of dry powders.

**Aerosolized antibiotics: uses and efficacy**

Many antibiotics are routinely given as aerosols to patients with cystic fibrosis (CF), including aminoglycosides (e.g., tobramycin and amikacin), colistin and aztreonam. A number of other antibiotics (e.g., the fluoroquinolones, ciprofloxacin and levofloxacin) are also in development for aerosol use.⁵ These and other antibiotics are being given to patients with ventilator-associated pneumonia (VAP), as well as to patients with multidrug-resistant bacterial infections when the minimal inhibitory concentrations exceed those that can be safely achieved intravenously.⁶ Aerosolized antibiotics are likewise being used in patients with limited IV access and inability to take oral medications, e.g., premature infants.

Studies of aerosolized drug delivery, mostly done in neonates, have identified a number of drug delivery related factors that can influence the efficacy of aerosolized delivery, including particle size, flow rates, and device placement with respect to the patient.⁷ There are major differences in the performance of different methods and devices used to generate aerosols (e.g., jet versus ultrasonic nebulizers) with respect to these factors. There are also drug, concentration and formulation factors that affect the efficiency of drug delivery to the patients and which, therefore, can affect how much of an administered drug is swallowed versus inhaled, as well as how much drug is vented into the environment.⁸ For these reasons, studies of aerosolized administration must control for drug/device-related differences.

In addition, there may be concentration-independent, drug-specific effects on the efficacy of inhaled drug delivery. Experimental evidence in rodents shows that fluoroquinolones are more effective when aerosolized because they achieve high pulmonary fluid concentrations.⁹ However, other authors have questioned whether there is any biopharmaceutical advantage to nebulization versus intravenous use.¹⁰ These authors claimed that the several-fold increases they observed in rodent pulmonary fluid-to-plasma concentration ratios of three fluoroquinolones were not the result of inhalation use, but rather the result of pulmonary efflux transporters that concentrate fluoroquinolones in pulmonary fluid. Clearly more studies are needed to establish, in humans, which nebulized drugs are more effective and why.

**Research needed**

There are a number of other unknowns and concerns about the use of nebulized antibiotics. For example, aerosols increase environmental contamination. Skin punctures, for example, cannot be used to collect blood to monitor
aminoglycoside concentrations in CF patients who use face mask-aerosolized antibiotics because their fingers are contaminated with the aerosolized drug. While less of a problem with ventilator-administered drugs, contamination of the environment as well as health care workers can occur. Also, drug that is swallowed rather than inhaled (a variable that is not an insignificant percentage of the administered dose) exposes the patient’s oral and GI track mucosal bacteria to the drug and potentially, to those who handle the patient’s bodily fluids, stool, urine and waste. The fact that higher concentrations and total amounts can be used is an advantage therapeutically, but it is also a potential disadvantage with respect to the development of resistance. Effects on the exposure of health care workers, including cleaning staff, are particularly in need of study.

There is very little known about the relative incidence of antibacterial resistance following inhalation compared with oral or intravenous administration. However, while concerns were raised when inhalation antibiotics were first used for CF patients, there has not been evidence yet of any increase, and it is at least theoretically possible that being able to use higher concentrations at the site of infection could actually decrease the development of resistance. Inhaled drugs are, as mentioned, being used successfully to treat multidrug-resistant pulmonary infections, which could subsequently decrease the spread of such organisms. Much needs to be done to clarify the relative risks of oral, IM, IV and inhalation use of antibiotics with respect to the development of resistance.

Toxicity of chronic pulmonary exposure to aerosol excipients is another concern. Bronchospasm can occur for example and must be monitored for, but its recognition can be delayed, especially in ventilated patients. Exposure to aerosols could also be a problem for staff that are allergic to the administered drug or its excipients.

Conclusions

Aerosolized antibiotics are being increasingly used based on the fact that this mode provides a way to deliver higher concentrations of drugs to the site of infection, as well as to administer drugs or amounts that cannot be given safely by oral or intravenous use. However, there are a number of unknowns associated with inhalation therapy, including environmental impacts and the effects of medical staff exposure.

Dr. Walson is a member of the APUA Board of Directors. He is also a paid consultant to Aerogen, a company that manufactures aerosol devices for medication delivery.

References:

APUA Headquarters in Action

**APUA staff attend Longitude Prize informational meeting**

The Longitude Prize is a science challenge with a £10 million prize fund which aims to conserve antibiotics for future generations and revolutionize the delivery of global healthcare. Prize administrators, including Professor of Health Law Kevin Outterson of Boston University School of Law, described the qualities judges sought in entries at a Harvard Business School promotional meeting. APUA’s Dr. Thomas O’Brien and Jane Kramer participated in the September event.

The Prize commemorates the 300th anniversary of the Longitude Act of 1714 when the British government challenged the public to solve the greatest scientific challenge, determining longitude at sea. In partnership with the BBC, the public voted for one of six of the biggest challenges today and chose antibiotic resistance to be the focus of the Longitude Prize in 2014. The challenge is to develop a point-of-care test that will identify when antibiotics are needed and if they are, which ones. Find out more about how you can get involved at longitudeprize.org. Entries are still being accepted.

**Clorox partners with APUA**

On September 3rd, Clorox Healthcare issued a press release announcing its new partnership with APUA to raise awareness on the link between antimicrobial stewardship, environmental hygiene and infection control practices.

“Ours is a natural alliance because strengthening health systems and clinical practice by cleaning, disinfection and process compliance reduces or prevents transmission of resistant bacteria. There are strategies that APUA champions globally and Clorox Healthcare helps realize,” said Stuart B. Levy, MD, President of APUA.

“APUA and Clorox Healthcare will work together to raise awareness of this important issue and strengthen educational programs that inform best practices in infection prevention and antibiotic stewardship,” said Rosie Lyles, MD, MHA, MLSc, Head of Clinical Affairs for Clorox Healthcare.

**APUA supports multiple legislative initiatives**

♦ APUA has added its support to the bi-partisan bill introduced into the U.S. Congress on Sept. 17. The "Reinvigorating Antibiotic and Diagnostic Innovation (READI) Act" would provide a tax incentive for qualifying manufacturers to increase clinical testing of antibiotic and antifungal drugs and rapid diagnostics for infectious diseases. Signed by over 40 supporting organizations, the letter emphasizes the need for new antibiotic development and the need to provide incentives to spur this work. Read the Text for H.R. 3539 here.

♦ In July, APUA, along with allied organizations, wrote to U.S. Representatives Lamar Alexander and Patty Murray urging them to include the bi-partisan “Promise for Antibiotics and Therapeutics for Health (PATH) Act” into broader legislation they are developing for the Innovation for Healthier Americans Initiative. Read the S.185 PATH Act here.

♦ APUA has joined with Pew Charitable Trusts and other interested organizations in signing on to a letter in support of the Centers for Medicare and Medicaid (CMS) proposed rule (Federal Register CMS-3260-P) that would make stewardship programs a condition of participation for long-term care (LTC) facilities. Because long-term care residents are often prescribed antibiotics, LTC facilities should implement antibiotic stewardship programs to monitor and ensure appropriate antibiotic use.

**Transitions**

APUA extends its deepest thanks to Dr. Gordon W. Grundy as he completes 12 years of outstanding service as a member of APUA’s Board of Directors. His leadership, advice and enthusiasm have aided the organization immeasurably in forwarding its mission to preserve the power of antibiotics. As he leaves our Board we wish him well in all his future endeavors. Thank you Dr. Grundy!
International Chapter Updates

Chapter Spotlight: APUA-Bulgaria

**Founded:** 1998

**Leadership:**
*President:* Prof. Encho Savov, MD, PhD, DSc; Head, Dept. Military Epidemiology and Hygiene, Military Medical Academy, Sofia
*Co-ordinator:* Prof. Emma Keuleyan, MD, PhD; Head, Dept. Clinical Microbiology, Medical Institute Ministry of the Interior;
Assoc. Prof. Kalinka Bojkova, MD, PhD Head, Dept Microbiology and Virology, Medical University, Varna?
Prof. Marianna Murdjeva MD, PhD, Vice-Rector on Scientific affairs;
Assoc. Prof. Boyka Markova, MD, PhD Head, Clinical Microbiology Laboratory "Sinevo", Sofia

**Affiliations:**
Bulgarian Society for Medical Microbiology (BSMM), the Bulgarian Association of Microbiologists (BAM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), European Society of Chemotherapy (and) Infectious Diseases (ESCiD), International Society of Chemotherapy (ISC) and others.

**Membership:** 105

APUA-Bulgaria chapter specialists in Clinical Microbiology, Epidemiology and Infectious Diseases organized and/or participated in the following scientific events during the first half of 2015:

- The scientific conference *Particularly Dangerous Zoonoses in Bulgaria*, held in Kostenec, March 17-18, 2015, (organized by the National Center for Infectious and Parasitic Diseases);
- The 8th National Congress of the Bulgarian Association of Microbiologists, Sofia, 16 - 18 April, 2015; and
- The Jubilee scientific conference *70 years of Medical University – Plovdiv*, Plovdiv, May 21-23, 2015.

Emerging severe zoonanthropoanoses was one of several featured topics. Of note, 400 confirmed clinical cases of Tularemia were recorded in Bulgaria during the past 10 years, with seven new cases appearing since the beginning of 2015; 21 cases of Crimean-Congo hemorrhagic fever occurred over 4 years, but only one case of anthrax during the last decade. During 2014 the preparation for, diagnosis and management of potential Ebola viral disease received special attention, together with measures for infection control. Among vector-borne infections, there were 404 cases of Lyme borreliosis, 343 cases of Mediterranean spotted fever and 17 cases of Q fever in 2014.

Within clinical bacteriology sessions, the most important focused on molecular mechanisms of antimicrobial resistance, particularly carbapenem resistance. Researchers have identified KPC-2 carbapenemase, VIM-1, OXA-48 and NDM-1 in *Enterobacteriaceae* strains, and Bla OXA23, OXA58 enzymes together with hypersecretion of OXA51 in *Acinetobacter baumannii*.

It is worth noting that antibiotic policies have been developed in all hospitals as a national state requirement. Both microbiologists and infectious diseases specialists are active participants in scientific projects and forums dedicated to preventing antimicrobial resistance. *European Antibiotic Day* is traditionally celebrated on November 18 and Medical University professors participate with specialized lectures and exercises on the issue.

In conclusion, Bulgarian microbiologists, epidemiologists and infectious diseases specialists share concern about the problem of antimicrobial resistance and work to prevent further development and spread. We seek to work with our international colleagues to contribute to resistance containment.

Prof. Encho Savov
President, APUA-Bulgaria
Members of the APUA-Bulgaria delegation

APUA – South Africa

Submitted by: Sabiha Essack, B. Pharm., M. Pharm., PhD

South Africa published its Antimicrobial Resistance (AMR) National Strategy Framework 2014-2024 in October 2014. This framework provides “a structure for managing AMR to limit further increases in resistant microbial infections and improve patient outcomes” via four strategic objectives:

- Establish national and health establishment governance structures to strengthen, coordinate and institutionalize interdisciplinary AMR efforts;
- Expand surveillance and early detection of AMR and enable reporting of resistance trends at local, regional and national levels to optimize empiric and targeted antibiotic choice;
- Enhance infection prevention and control to contain the spread of resistant microbes to patients in healthcare
settings, focusing on hand hygiene and patient isolation (Community measures include preventing infection through vaccination programmes and improvements in water and sanitation); and

- Implement antimicrobial stewardship to promote appropriate use of antimicrobials in human and animal health.

Health system strengthening is acknowledged as central to the success of the strategy and the interventions are underpinned by education (of health professionals within undergraduate and postgraduate curricula, as well as via continuous professional education courses), public awareness and a sustained multi-pronged communication and information campaign. Oversight and governance are mooted to ensure that the strategy is implemented in all relevant sectors.* Signatories to the Framework are the government Ministries of Health, Science and Technology and Agriculture Forestry and Fisheries, private and public Laboratory Services, Professional Societies, Regulatory Bodies and Civil Society. An implementation plan has been drafted using a results management framework which delineates outcomes, outputs, activities, indicators, time frames and responsible offices/persons as well as risks and risk mitigation strategies. The call for nominations for the Ministerial Advisory Committee which will have oversight of the implementation of the AMR framework is imminent.


Caruffo & Navarrete Refs cont. from p. 7


2015 Get Smart Week is November 16-22

Get Smart About Antibiotics Week is an annual one-week observance to raise awareness of the threat of antibiotic resistance and the importance of appropriate antibiotic prescribing and use.
**Resistance in the News**

**Point-of-care CRP test shows promise for reducing antibiotic prescriptions**

The UK group, Patients’ Association, has published a report which reveals that the use of point-of-care (POC) C-reactive protein could potentially reduce the number of antibiotic prescriptions by 10 million. The use of this test would also save the NHS £56 ($87.3) million in associated prescription and dispensing costs. The test is very simple, requiring a finger-prick blood sample with results available in a few minutes to help determine whether or not antibiotics are appropriate for treatment. The report further states that “despite the findings that POC CRP testing reduces inappropriate and unnecessary antibiotic prescribing in primary care…the UK continues to limit its use of the testing method”.

The report goes on to make recommendations for policymakers, commissioners, and health professionals including:

- **Routine use of POC CRP testing by health professionals and its integration into patient consultation;**
- **Recognize the POC CRP testing could help clinical commissioning groups attain the Quality Premium and meet the NHS quality agenda;**
- **Follow NICE guidelines for pneumonia, which supports combining primary care CRP POC testing with clinical diagnosis and history-taking to decide whether to prescribe antibiotics for lower respiratory tract infections; and**
- **Collaborate with commissioners to develop local guidelines that support accurate differential diagnosis for respiratory tract infections.**


**Garlic compound shows promise in fight against multidrug-resistant pathogens**

Scientists at the Birla Institute of Technology and Sciences in India have discovered that garlic, *Allium sativum*, has properties that are effective in fighting multi-drug resistant bacteria that cause urinary tract infections (UTIs). More specifically, the chemical allicin, which gives garlic its signature scent and works to repel natural predators, is thought to be the key to the herb’s antibiotic properties.

Published in *Pertanika Journal of Tropical Agricultural Science*, the article, *Garlic: An Effective Functional Food to Combat the Growing Antimicrobial Resistance*, describes a study of urinary tract pathogens (*E. coli, Enterobacter sp, Klebsiella sp. S. aureus, and P. aeruginosa*) with multidrug resistance to ≥4 of 7 agents tested. When exposed to allicin extract in Kirby-Bauer disk diffusion assays, 82% of strains showed susceptibility to the chemical.

An earlier article in *PlosOne* (*Garlic revisited: antimicrobial activity of allicin-containing garlic extracts against Burkholderia cepacia complex*) suggests that allicin has potential as an adjunct to existing antibiotics in the treatment of the intrinsically antibiotic-resistant *Burkholderia* infections that plague cystic fibrosis patients.

The promising results are encouraging researchers to explore alternatives to the current cache of antimicrobials and to investigate a crucial factor—whether oral administration or injection provides the most effective delivery.

**“Weaponized” Acinetobacter demonstrates self-limiting resistance**

In a recent PNAS study, researchers at the Washington University School of Medicine in St. Louis suggest that drug-resistant bacteria can be self-limiting. The researchers focused on multidrug-resistant *Acinetobacter baumannii*, a leading hospital-acquired bacterium that also survives disinfectants,
making it very difficult to treat. This organism carries a toxic type VI secretion system (T6SS) that acts as a survival strategy against bacterial competitors. In most strains, the system is repressed by regulators borne on a self-transmissible resistance plasmid, which also expresses multidrug resistance (MDR). However, when subjected to a hostile environment, a subset of cells spontaneously lose the plasmid, which activates the T6SS, but results in simultaneous loss of the MDR phenotype. Further studies on samples from outbreaks across the globe showed the same pattern. The discovery that such superbugs could readily and naturally revert to susceptibility in the absence of selective pressure shows tremendous potential for the fight against antibiotic resistance. Senior author, Mario Feldman, stated “This knowledge could lead to more effective treatments and better strategies for preventing the development of superbugs”. Read more here.

**Common antacid shows promise in combatting multidrug-resistant tuberculosis**

In 2013, tuberculosis infection (caused by *Mycobacterium tuberculosis*) resulted in 9 million new infections and 1.5 million deaths globally. Second only to AIDS as the greatest cause of global mortality, TB persists widely due to its multidrug resistance. New drug development is very costly, involving lengthy clinical trials, which has prompted scientists at the Ecole Polytechnique Federale de Lausanne to adopt an alternative strategy.

Using robotized, high-through-put assays, the scientists screened previously approved chemicals for a possible solution and identified lansoprazole as a potential anti-TB drug. Also known as Prevacid® commercially, lansoprazole is an over-the-counter antacid found to kill the pathogen after the drug had been converted into a sulfur-containing metabolite by human lung cells. Further tests against a wide range of bacteria showed that the antacid was highly selective for *M. tuberculosis*. This fact, in combination with its safety record and global accessibility, makes lansoprazole a highly attractive candidate for combatting the global scourge of TB.

Read the paper published in *Nature Communications*.

**CDC issues 5-pronged Antibiotic Resistance Solutions Initiative**

The U.S. Centers for Disease Control and Prevention (CDC) are central to the Obama Administration’s National Action Plan for Combating Antibiotic Resistant Bacteria (CARB). As such, $264 million has been earmarked for the agency’s comprehensive response to fighting resistance.

The response strategy, aptly named the **Antibiotic Resistance Solutions Initiative**, is comprised of 5 “core actions”:

- Slow the development of resistant bacteria and prevent the spread of resistant infections
- Strengthen National One-Health Surveillance efforts to combat resistance
- Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria
- Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines
- Improve international collaboration and capacities for antibiotic resistance prevention, surveillance, control, and antibiotic research and development

The plan was unveiled as a result of the White House Forum on Antibiotic Stewardship held in early June. The CDC’s initiative is part of a wider national strategy that aims to improve the capacity of states to respond to, track, and prevent antibiotic misuse and decrease resistance. Visit the CDC website for more information.

**New susceptibility testing paradigm offers hope for more effective antibiotics**

Using a novel approach to test for antimicrobial susceptibility, researchers at the University of California Santa Barbara have uncovered the possible reason why some bacteria test "susceptible" in standard laboratory tests, but fail to respond to treatment in patients. Conventional antimicrobial susceptibility assays are performed in a standard test medium (Mueller-Hinton) with a pH of 7.2. In experiments with a culture medium which more closely resembles intracellular
UK study reveals poor comprehension of antibiotic resistance issue

In an interview with BBC Radio, UK Chief Medical Officer, Dame Sally Davies, made the bold statement that “Modern medicine, as we know it – if we don’t halt the rise of resistance – will be finished.” She spoke in response to a recent report published by the Wellcome Trust (Exploring the consumer perspective on antimicrobial resistance) which revealed that public understanding of resistance is very low in the UK. The researchers found that most study participants wrongly believed that resistance was caused by their bodies growing immune to antibiotics, rather than being caused by antibiotic-resistant bacteria. Another popular misconception was the fact that individuals thought because they didn’t misuse/abuse antibiotics, resistance would not be a problem for them.

Lead researcher, Michael Mahan, noted a need for “lab drug sensitivity testing to incorporate media that mimic the specific biochemical environments that trigger resistance in the body.” If the millions of chemicals held in pharmaceutical libraries were rescreened using different media, it could open up a world of more effective compounds for tackling the antibiotic resistance problem.
Clearly, such erroneous thinking at the population level is an indicator of the lack of awareness of what resistance is and the factors that contribute to it. Without a targeted campaign of raising the public awareness and providing general practitioners the tools to properly educate their patients, resistance will continue to rise. Currently, around 25,000 people across Europe die due to infections caused by antibiotic-resistant bacteria. Experts have projected that this number will increase drastically if the trend of rising resistance is not curbed and reversed.

**CDC reveals encouraging outcome for integrated stewardship intervention**

Hospital-acquired infections (HAIs) caused by antibiotic-resistant bacteria, including *Clostridium difficile*, continue to plague U.S. hospitals, with limited options for effective treatments. However, as announced in CDC’s latest Vital Signs post, a modelling study involving actual healthcare facilities reveals hope for interrupting the spread of HAIs if coordinated approaches between health facilities are employed.

Data from the agency’s National Healthcare Safety Network and Emerging Infections Program were analyzed to project the number of HAIs, both with and without concerted intervention methods. Results showed that immediate nationwide infection control and antibiotic stewardship efforts could avert an estimated 619,000 HAIs (CRE, MDR *Pseudomonas aeruginosa*, MRSA and *C. difficile*) over a 5-year time period. Compared to stand-alone interventions, a coordinated response against carbapenem-resistant *Enterobacteriaceae* (CRE) would result in a 74% reduction in acquisitions over 5 years in a 10-facility model, and a 55% reduction over 15 years in a 102-facility model.

PEW reveals findings on antibiotic development

In late July, The Pew Charitable Trusts issued a brief on the research and development of antibiotics: Tracking the Pipeline of Antibiotics in Development. With antibiotic resistance on the rise globally, it is imperative to have a “robust pipeline of new drugs and innovative pathways to get this medicine to the patients who need it most.” Unfortunately, new drug development requires extensive research, is cost-intensive, and requires years. It is estimated that only 1 out of 5 drugs that reach initial testing phase in humans achieves approval from the Food and Drug Administration. As such, the pharmaceutical industry has been wary of investing in antibiotic development in recent decades.

Pew has assessed drugs that are currently in clinical development and reported the following findings:

- 36 antibiotics are currently in development; 8 are in phase 1 clinical trials, 20 in phase 2, and 8 in phase 3 (~60% of phase-3 drugs receive approval). (View table.)
- At least 11 of the antibiotics have the potential to treat the ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter, Pseudomonas aeruginosa, and Enterobacter). If approved, 16 or more antibiotics could address CDC’s “urgent threat” pathogens (resistant N. gonorrhoeae, C. difficile, and carbapenem-resistant Enterobacteriaceae).
- At least 2 antibiotics in early development attack bacteria in novel ways by sidestepping current resistance mechanisms. Others attack traditional targets with new chemical compounds.
- Out of 31 companies with antibiotics in development, only 5 rank among the top 50 pharmaceutical companies by sales. Three-quarters of new antibiotics are being developed by small companies, of which ~40% are “pre-revenue.”

The complete brief can be accessed here.

For more information on novel approaches to drug development, see the article by Kim Lewis in the spring 2015 issue of the APUA Newsletter (Vol 33, No 1).

UK releases One Health Report: Joint report on human and animal antibiotic use, sales and resistance, 2013

Acknowledging the need for a “One Health” approach to the antibiotic resistance problem, Public Health England recently published a report on the current state of antibiotic resistance in the UK. It details the quantities of antibiotics used in human health and animal welfare with the aims of:

- Encouraging further collaboration between the human and animal sectors;
- Identifying the emerging and current antibiotic resistance threats in three key bacteria in both humans and animals
- Identifying differences in surveillance methodology and data gaps that limit our ability to compare trends between the two fields, both within the UK and across Europe;
- Evaluating available data from humans and animals side by side and beginning assessment of the relationship between antibiotic sales, use and resistance across the two sectors;
- Developing recommendations to improve the surveillance of antibiotic use and resistance in humans and animals.

The report highlights the fact that data collection across the country varies so markedly that it becomes impossible to make meaningful comparisons. This underscores the need for greater collaboration between human and animal health sectors in order to properly tackle antimicrobial resistance. The report identified Escherichia coli, Campylobacter, and Salmonella as the top problematic bacteria for both human and animal health, and proffers ten recommendations for governmental action. A future report will provide update on progress.

Read the full report here.
Special journal edition focuses on global collaboration to address antimicrobial resistance

The Journal of Law, Medicine & Ethics has published a special summer volume titled *Antibiotic Resistance* (co-guest edited by Steven J. Hoffman and Kevin Outterson), which focuses on how a global collaborative effort can address the urgent problem of increasing antimicrobial resistance. Specifically, it features a dozen articles in which the various authors issue a call for a general international consensus on antibiotic policy and “argue that such an agreement should address access, surveillance, prevention, infection control, the needs of the under-served, accountability, and which forums, such as the WHO, can help facilitate this policy”. In producing this volume the editors state that “Our real innovation here is having taken a scientific approach to global strategy whereby we drew upon a range of disciplines to systematically assess how instruments, institutions and initiatives could be designed to foster collective action on ABR and maximize impact.”

This edition is the first of its kind for the Journal and is available online only.

For more on this topic, see the following:

*Repairing the broken market for antibiotic innovation* by K Outterson, JH Powers, GW Daniel & MB McClellan. Health Affairs 2015. 34: 277-285. [http://content.healthaffairs.org/content/34/2/277.full.html](http://content.healthaffairs.org/content/34/2/277.full.html)

UK report summarizes contribution of behavioral science to antibiotic stewardship

In a Feb. 2015 report titled *Behaviour change and antibiotic prescribing in healthcare settings: literature review and behavioural analysis*, Public Health England and the Department of Health issued strong support for using behavioral science to address the problem of high rates of antibiotic prescribing. The report reviews and summarizes the available evidence on behaviors that drive resistance—analyzing perspectives from patient use, prescribers, and primary and secondary care. Using a theoretical domains framework, the authors modeled a ‘behavioral analysis,’ which identified key behaviors and drivers that can become a focus for change.

The report considers 15 intervention opportunities as follows—dividing them into those that are achievable within different time frames:

**Short-term**
- Feedback on prescribing behaviors
- Online pledges for parents
- Improving the TARGET antibiotic leaflet*

**Medium-term**
- Substitution of antibiotic therapy
- Reducing patient appointments for self-limiting infections at GPs
- Advising patients on their antimicrobial usage
- Adding friction to prescribing
- Guideline implementation and decision support
- Making back-up prescribing the default for respiratory infections
- Improving the presentation of the TARGET clinical guideline
- Recording GP decision-making
- Design-led hospital prescription charts

**Long-term**
- Making antibiotic packaging salient
- Presenting resistance as a societal threat
- Increasing the cost of antimicrobials

*A component of the Royal College of General Practitioners’ TARGET Antibiotics Toolkit; TARGET = Treat Antibiotics Responsibly, Guidance, Education, Tools*
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 65 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.

The APUA Newsletter has been published continuously three times per year since 1983.
Tel: 617-636-0966 • Email: apua@tufts.edu • Web: www.apua.org

APUA global chapter network of local resources & expertise

136 Harrison Ave, M&V Suite 811, Boston, MA 02111
Phone: 617-636-0966 | Fax: 617-636-0458 | E-mail: apua@tufts.org

www.apua.org