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Global Food Animal Use of Antibiotics

This graph maps for the first time, estimates of animal antibiotic use on a global basis. (in milligrams per 10 km² pixels; 2010). Click here for news updates on antibiotics in food animals.
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Bacteriocins: peptide antimicrobials with therapeutic promise

Colin Hill, APC Microbiome Institute, University College Cork, Ireland

Most bacteria live in complex communities and have to compete for scarce resources. While it has been long known that some bacteria were capable of producing antimicrobials, perhaps the earliest report of inhibition that we can ascribe to a bacteriocin was made by Rogers in 1928, who observed that *Lactococcus lactis* was capable of inhibiting the growth of *Lactobacillus bulgaricus*.\(^1\) We now know that this was due to the production of nisin. To date, bacteriocins such as nisin have been largely deployed in food rather than in medicine,\(^2\) although there are some examples where bacteriocins have been successfully used in animal health. However, the ongoing crisis with respect to antibiotic resistance in clinical settings has led to a renewed interest in using bacteriocins in human therapy.\(^3\) Bacteriocins are antimicrobial peptides which precisely fit the original definition of antibiotics proposed in 1947 by Selman Waksman as “a chemical substance, produced by micro-organisms, which has the capacity to inhibit the growth of and even to destroy bacteria and other micro-organisms”.\(^4\)

An example of bacteriocin production is presented in Figure 1, where a bacteriocin produced by a *Lactobacillus* colony is capable of inhibiting a lawn of *Listeria monocytogenes* growth on an agar plate. From the agar plate it is obvious that bacteriocins are secreted—small and soluble—and also it is noteworthy that no resistant colonies are observed within the zone of inhibition. Bacteriocins share some basic characteristics. First, they are (usually) gene-encoded peptides which are exquisitely active against their target species (they can be either narrow— or broad-spectrum), and they often have minimum inhibitory concentrations in the single nanomolar range (many times more active than most frontline antibiotics). Second, the producer cell possesses a dedicated immunity mechanism to prevent self-destruction. Third, bacteriocins usually target the cell envelope of sensitive cells. While most bacteriocins share these characteristics, there are two main categories worth describing. The unmodified (usually termed Class 2) bacteriocins are essentially simple peptides, which typically act by binding to receptors and inserting in the membrane to form a pore. Class 1 includes the heavily post-translationally modified bacteriocins such as nisin, which contains lanthionine residues formed from linkages between serine (or threonine) and neighboring cysteine residues. Nisin has been shown to

![Figure 1. Bacteriocin activity](image-url)
have a dual mechanism of action, first binding to lipid II and then inserting into the membrane to form a pore. The lantibiotics (lanthionine-containing antibiotics) are usually broad-spectrum, and can be active against many Gram-positive species. Because of their gene-encoded nature, bacteriocins also lend themselves to genetic engineering to create banks of variants, which can be mined for additional properties and activities (Figure 1).

Perhaps the greatest asset of bacteriocins—their extremely potent activity—is also their greatest barrier to widescale deployment, in that these inhibitory molecules are produced in relatively low quantities, making their development as therapeutics problematic. However, if these problems are overcome, bacteriocins have considerable potential as alternatives or adjuncts to antibiotic therapy.

We have shown that bacteriocins can work in vivo in a trial conducted to prevent bovine mastitis by incorporating a food-grade lantibiotic, lacticin 3147, into a teat seal. Teat seals are physical barriers composed of bismuth subnitrate used to prevent pathogens from gaining access to the mammary gland. A teat seal was formulated which included lacticin 3147, and animals were subjected to a deliberate infection with a mastitic pathogen, Streptococcus dysgalactiae. The results were very encouraging in that almost 50% of the animals with teat seal alone developed clinical mastitis, whereas only 9% of the animals with teat seal containing the bacteriocin went on to develop the disease. Bacteriocins can also be delivered in situ by the producing bacterium, perhaps in the form of custom probiotics. For example, a Lactobacillus salivarius strain producing a bacteriocin (abp118) can successfully prevent Listeria monocytogenes infection in a murine model. This is entirely due to the bacteriocin, since a bacteriocin knockout strain offers no protection against infection (Figure 2). This offers a potentially low cost solution to the problem of bacteriocin delivery at the site of infection.

Another variation on this theme is the concept of replacement therapy, in which an avirulent pathogen can utilise bacteriocin production to outcompete its virulent relatives. This has been described for a mutacin-producing avirulent variant of Streptococcus mutans, which can colonise the oral cavity and prevent further colonisation by a virulent counterpart. Much of the early research on bacteriocins focused on broad-spectrum molecules, but the growing realization of the importance of the human microbiome, together with the recognition that non-target species can develop resistance to broad-spectrum agents, has rekindled interest in narrow-spectrum bacteriocins. We have identified a novel bacteriocin, thuricin CD, which can ‘treat’ Clostridium difficile in an ex vivo model of an infected colon. Interestingly, in ex vivo colonic model systems, this narrow-spectrum bacteriocin proved as successful as either vancomycin or metronidazole in killing Clostridium difficile, but without inflicting significant collateral damage on the microbiome (Figure 3). Such targeted action may well be appropriate as we begin to appreciate the importance of a diverse microbiome to human health. Perhaps
one future aspect of antibiotic deployment will involve the judicious use of narrow-spectrum antimicrobials such as bacteriocins, or probiotic strains producing bacteriocins, both to avoid widespread resistance development and to avoid damaging this sophisticated human niche.

Bacteriocins are not a panacea for the problems of antibiotic resistance, but they do provide an interesting and valuable alternative or adjunct therapy. Many bacteriocins are very effective against biofilms, or can potentiate antibiotic efficacy, at least in the laboratory, and this could be the basis of future therapeutic options.

Figure 3. Bacteriocin activity

Narrow-spectrum bacteriocin activity in a colonic model of *Clostridium difficile* infection. The graph shows the effect of metronidazole and thuricin on reducing the pathogen numbers in the artificial colon, while the pie charts illustrate the impact on the microbiome at the phylum level.

References:


With increasing political commitment to address the problem of antimicrobial resistance (AMR) in recent years, there has also been a shift towards a more interdisciplinary approach to the issue. It is now widely accepted that a comprehensive response to AMR will involve not just new antibiotics or improved prescription guidelines, but that a ‘whole of society engagement’ will be necessary, as the Global Action Plan on AMR puts it. This will for instance include the creation of greater public awareness of AMR and a change in behavior for both prescribers and consumer. It has therefore been positive to see that research areas not traditionally concerned with AMR are increasingly becoming involved in the scientific and public discourse.

One area that has so far received less attention, however, is the analysis of ethical questions that arise in the context of AMR. This article will provide a brief overview of what these questions are, and why they matter.

**Some fundamental ethical concerns about AMR**

While ethical questions are perhaps not the first ones that come to mind when considering drug resistance, AMR actually raises a broad range of ethical concerns. These can be divided into at least four distinct areas.

First, AMR exacerbates existing ethical dilemmas in infectious disease control, by making infectious diseases more difficult to treat. Infectious disease control, and the measures it necessitates, have long been one of the key areas of medical ethics. They relate, for instance, to the isolation of contagious patients, the treatment of patients against their will, or the protection from disease that health care workers are entitled to. As bacterial diseases become more difficult to treat as a result of AMR, the relevance of many of these questions is amplified for health care workers and patients alike. However, in these instances existing ethical issues simply become more pressing – the underlying questions themselves have not changed.

Second, AMR raises questions about the fair distribution of resources within and between countries. With the emergence of more resistant infections, especially in resource-limited settings, many weak health care systems are being pushed to their limits. We must therefore discuss to what extent high-income countries have obligations to extend access to effective drugs to low-income settings and to assist countries whose healthcare systems are insufficiently equipped to deal with AMR themselves.

A third ethical concern relates to the use of antibiotics in animals. On the one hand, the overuse of antibiotics in the animal sector has been cited as one of the key reasons for the emergence of AMR. On the other hand, the world population is growing rapidly and relies heavily on access to affordable meat. Substantial changes to the existing system may therefore come with serious consequences for many people, which must be weighed against the benefit we are hoping to achieve.

A fourth normative question that AMR raises is what we owe to future persons when it comes to the preservation of effective antibiotics. With a largely empty pipeline of new antibiotics, there are now serious worries that we may enter a 'post-
antibiotic age’, in which some bacterial infections are no longer treatable. This raises complicated questions about the rights of future persons and the corresponding obligations we are under to preserve antibiotic effectiveness. Yet, if future persons have a right to effective antibiotics, does this mean that we must drastically limit their use today, in order to slow down the emergence of AMR as much as possible? These are difficult questions to answer, and few have so far attempted to integrate them systematically into policy discussions.

Trading off risks, costs and benefits

At the heart of many of the problems that have been mentioned so far lies the need to make decisions about the distribution of risks, costs and benefits across people and time. Making even the most powerful antibiotics cheaply available to consumers in health care systems that are poorly regulated and where many drugs are sold without a prescription will, for example, likely speed up the emergence of AMR. But it may also give patients in these regions access to effective treatment if they have contracted a resistant infection that can no longer be treated with the drugs that are currently available to them. It should also be noted that in many countries, it is not the overuse of antibiotics but the complete lack of access to them that is currently the greatest burden to health.4

We also face difficult decisions about the acceptable risks to patients in high-income countries when deliberating how to reduce the use of antibiotics. While in some instances, overuse may be easy to identify and address, the reduction of antibiotic can also come at some additional risk of complication or prolonged disease to the patient. These risks may not always be substantial, but they exist nevertheless. And in some instances, they have been shown to be rather significant. In a review article of guidelines for the treatment of community-acquired pneumonia, for example, the authors showed that the IDSA’s recommendation that macrolides should be used as first-line therapy up to a 25% rate of high-level resistance resulted in excess mortality of 1%.5 It may indeed be the case that the restriction of antibiotic use and the elimination of inappropriate prescribing make it necessary to accept higher risks. But where this threshold should lie, and what is an acceptable risk to the individual are deeply normative questions that we have so far failed to address appropriately.6

Integrating ethical considerations into policy-making

Many of the ethical problems discussed in this article elude easy answers and instead raise uncomfortable questions about what we are willing to do for one another and for future persons. However, this should not lead us to ignore them. Failing to address the ethical questions that AMR raises is no way to avoid them – our attempts to address the problem will invariably have ethical implications of the kind I have described. What we should therefore aim for is to better integrate ethical deliberations into the policy-making process and to raise awareness for them among prescribers. This will probably not make it easier to solve these problems – but it will make the decisions we make to address them more transparent. And it should hopefully help us to alert all stakeholders to the importance of ethics in the context of AMR.

References


PYA—Rolling Back the Resistance Clock

To many in the healthcare industry, it may be surprising that PYA (Pershing Yoakley & Associates, P.C.), with decades-old roots as a traditional accounting and consulting firm, would have an interest in, or be involved with, a public health issue like antibiotic resistance. Since its beginning in 1983, PYA has grown considerably and steadily broadened its scope of services. While PYA continues to serve clients with their tax and audit needs, it is better known within the healthcare industry for its consulting and management advisory services. More specifically, the firm’s operational, financial, and strategic planning advisory services for healthcare clients have been most prominent.

So, how and why is PYA a part of the effort to fight antibiotic resistance? The readers of this newsletter are likely well aware of the negative consequences of poor antibiotic usage patterns and the rising trend of using broad spectrum antibiotics.

As trusted advisors, PYA recognized that an absence of affirmative antibiotic plans would have significant adverse consequences for the company’s clients and the communities that they serve; it would have the opposite effect of the “Triple Aim.”* Without an in-house remedy or experience in this specific area of clinical expertise, PYA looked elsewhere to find a solution.

Vision to Improve Public Health

Since PYA’s inception, Ed Pershing, founder and CEO, has had a vision of improving public health. In 2015, his vision—found manifestation in a group of individuals dedicated to effectuating meaningful change in the way antibiotics are

Figure 1. Approaches towards reduction of infection risk

*Escherichia coli, Klebsiella pneumoniae
utilized in the healthcare industry.

This team, led by James M. Keegan, MD, is comprised of individuals with various backgrounds in the healthcare industry (some clinical, some operational). In addition to a broad connection of healthcare experience, they shared one other important trait: they all have a passion for fighting antibiotic resistance from the inside out. Dr. Keegan, an infectious disease specialist, has been dedicated to this issue for nearly 20 years. PYA became aware of the excellent work being done by Dr. Keegan and his team in Western South Dakota; so in mid-2015, Dr. Keegan and his team became a part of PYA. Together, they decided to collaborate to combat the global issue of increasing antibiotic resistance and the ongoing misuse of antibiotics.

There is a steady supply of research that has helped bring awareness to the issue of antimicrobial resistance and its corresponding public health threats. From the use of antibiotics in agriculture to inappropriate antibiotic prescribing patterns in practices across the country, antibiotic resistance is a topic that is beginning to resonate with the general public. In the past year, national consumer brands like Tyson Foods, Subway, Chipotle, McDonald’s, and others have made pronouncements that they would severely restrict or eliminate the use of antibiotics in their products.

PYA’s vision for an effective antibiotic stewardship program is to utilize the research and hard work of professionals to change clinical behavior. Using a variety of mechanisms, our approach is to work collaboratively with hospitals, physicians, and other healthcare providers to develop responsible antibiotic prescribing patterns. Our goal is to slow, and even reverse, antibiotic resistance. In short, we espouse the philosophy of aggressive diagnostics and conservative therapeutics.

**Examples of Our Successes**

The key to success for the PYA model is a collaborative approach to addressing antibiotic stewardship with hospitals, physicians, and their communities. The model has worked in various settings, from a small rural community with an engaged community hospital, to a large, statewide initiative in the eastern United States.

*Dot* days of therapy
Source: PYA

![Figure 2. Broad spectrum fluoroquinolone DOT and *Clostridium difficile* (CDI) infection rates](image-url)

*DOT: days of therapy*  
(Source: PYA)
Community Hospital Initiative

Working in conjunction with the South Dakota Department of Health and a rural hospital and community for one year, we were able to decrease overall antibiotic usage and broad spectrum antibiotic usage. Participants included the community’s critical access hospital, a local clinic, a developmental center, two pharmacies, and two nursing homes. With a community focus on proper antibiotic usage and whether or not an illness needs antibiotic intervention, we decreased overall antibiotic use by 40%. There was a 59% reduction in broad spectrum antibiotic use, and a 53% reduction in antibiotic pharmacy costs. The data collected and analyzed during the year confirmed there was an overall decrease in bacterial resistance in this community. As a result, antibiotics prescribed and utilized at present are working better than they were one year ago (Fig. 1); this rural hospital and community rolled back the resistance clock.

Statewide Initiative

PYA began working with a state hospital association in the eastern United States last fall on a statewide antibiotic stewardship initiative. Hospital participation was not mandatory, but nearly 30 of the state’s hospitals elected to participate.

The goals of the project were modest, clear, and attainable: reduce overall antibiotic use by at least 10%, reduce broad-spectrum antibiotic usage by at least 10%, and, correspondingly, achieve cost savings for participating hospitals. Cost savings include direct savings on expenditures for drugs and the reduction of costs related to the incidence of *C. difficile*. Since antibiotic use and the incidence of *C. diff* are correlated, the attributed costs associated with this deadly healthcare-acquired infection are significant. The indirect financial benefits include decreasing readmissions and reducing length-of-stay metrics associated with hospital-acquired infections.

While still in the midst of the year-long initiative, the current results have been positive and have indicated early success (Fig. 2). Many facilities, in as few as six months, have made significant gains and already hit their year-end goals of reducing antibiotic usage by 10%. All facilities have made progress—some by improving internal processes, providing education and training, or engaging providers with multidisciplinary rounding. A number of hospitals have opted for a higher level engagement and are seeing enhanced and remarkable progress that exceeds set goals and expectations.

The Path Forward

PYA is committed to tackling antibiotic resistance utilizing a comprehensive, methodical approach, and has reduced antibiotic use and improved savings for multiple facilities. With the weight of an experienced team behind it, PYA will continue to fight what the Centers for Disease Control and Prevention estimates kills approximately 23,000 people in the United States annually. Many of the antibiotic-resistant infections originate in the hospital or other healthcare settings—a frightening reality for those who need those hospitals and other healthcare facilities to be a safe place for recovery from other conditions.

It will take time to turn back the clock, but PYA’s team is prepared to optimize patient treatment regimens, improve patient care, minimize costs, and positively impact health for whole populations.

*“Triple Aim”: improving the patient experience (quality and satisfaction), improving the health of populations, and reducing cost

PYA’s “Triple Aim”
APUA honors Leadership Award winner

On March 28, APUA staff, board members and colleagues gathered for a celebratory dinner in a local Boston restaurant to honor APUA’s most recent Leadership Award recipient, Professor Kevin Outterson of Boston University. APUA President, Dr. Stuart Levy recognized Dr. Outterson for his outstanding work as a leading scholar on the economic and legal framework needed to combat resistance and keep antibiotics available for future generations.

On Jan 30, 2016 Prof. Outterson chaired the American Journal of Law Symposium, Global Infectious Diseases: New Challenges and Solutions. He also recently co-edited a special supplement to the Journal of Law, Medicine and Ethics that was devoted entirely to the problem of antibiotic resistance and the need for an integrated global solution. In a newly published edition of Health Affairs, Drs. Outterson and Anthony McDonnell discuss the pros and cons of a proposed voucher system to reward antibiotic innovation and suggest solutions to minimize the current inequities that exist between public benefit and value to the company developer. Dr. Outterson’s other publications on antibiotics and the problem of antimicrobial resistance can be viewed here.

ASM’s Cultures publication highlights APUA and Tufts research center

The American Society for Microbiology has devoted the latest edition (Vol 3:1) of its quarterly publication, Cultures, to the question “Is antibiotic use in agriculture driving antimicrobial resistance?” Among discussions from noted experts on the topics of antibiotic stewardship, economics, antibiotics in agriculture, and food security, the volume shares the vision of the Tufts University Center for Adaptation Genetics and Drug Resistance and its partner non-profit organization, the Alliance for the Prudent Use of Antibiotics (APUA). While both were founded and spearheaded by Dr. Stuart B. Levy, the Center has focused on the basic mechanics of antibiotic resistance evolution and spread, and APUA emerged as a policy arm of the Center—acting for many years as a lone, vocal proponent for better antibiotic stewardship, especially in the realm of antibiotic use in food animals. The article describes how APUA ultimately evolved as a multifaceted vehicle for research and for mobilizing change in how we think about and use our antibiotic resources in homes, health-care facilities and on farms.

For current and previous issues of Cultures, visit http://www.asm.org/index.php/cultures-magazine.

APUA President Levy interviewed on “Wellness Wednesday”

On April 20, Dr. Stuart Levy and Dr. Patrick McNamara, Assistant Professor, Department of Civil Construction and Environmental Engineering at Marquette University, were interviewed on All Sides with Ann Fisher (WOSU Radio, Columbus, Ohio) on the topic of antibacterial soaps. The discussion focused on the health and environmental aspects of
antibacterial soaps, such as triclosan. In contrast to alcohol-based antibacterials, these components are becoming bioburdens with the unintended potential for building antiseptic and antibiotic resistance.

**APUA signs letter in support of FY2017 Budget Report**

In a letter directed to eight chairpersons and ranking members of the appropriations committees from both the U.S. Senate and House of Representatives, APUA and 47 other stakeholders—representing patients, public health, providers and industry—expressed their thanks for investment in the FY2016 appropriations to address the public health crisis posed by antimicrobial resistance. Importantly, the letter continued by asking for high priority emphasis on the sustained implementation of the National Action Plan for Combatting Antibiotic-Resistant Bacteria (NAPCARB) and specifically for budgetary support of the following FY2017 NAPCARB programs:

- Antibiotic Resistance Solutions Initiative (CDC): $200 million
- National Healthcare Safety Network (CDC) $21 million
- Advanced Molecular Detection (AMD) Initiative (CDC): $30 million
- National Institute of Allergy and Infectious Disease (NIH): minimum of $4.715 billion
- Biomedical Advanced Research and Development Authority (ASPR): minimum of $512 million
- Combating Antibiotic-Resistant Bacteria (AHRQ): $12 million

**APUA-supported stewardship bill suffers setback in California**

On February 10, 2016, Senator Jerry Hill of California introduced legislation into the California senate that would declare the legislature’s intent to promote the establishment of antimicrobial stewardship programs or policies in outpatient health facilities. The bill (SB 994) was supported by APUA and numerous other stakeholders interested in promoting antimicrobial stewardship policies as a means of preserving antibiotic efficacy and curbing the rise of antibiotic resistant infections. Regrettably, the bill was withdrawn due to “continued opposition from the medical community.” The bill would have built upon the successful efforts of SB 1311 (2014) and SB 361 (2015), which mandate stewardship programs in California’s acute care hospitals and skilled nursing facilities. SB 994 would have expanded the requirements to include outpatient care facilities, where much antibiotic overprescribing occurs, especially for acute respiratory infections.

**CHAPTER UPDATE: APUA – INDIA**

Dr. Abdul Ghafur of APUA-INDIA has informed us of the new “National Antibiotics Guideline” which was released by the Indian Ministry of Health during the recent International Conference on AMR in New Delhi. Development of the document faced challenges posed by a countrywide deficit in hospital surveillance data. Consequently it contains both narrow- and broad-spectrum antibiotic options for treating most infectious agents. The document is considered a “work in progress” and will be revised in six months, pending stockholder feedback. The new guidelines can be accessed [here](#).
**CARB advisory council issues first progress report**

In early April, the U.S. President’s Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) released its first report (March, 2016) on the progress made, and challenges faced, in responding to President Obama’s National Action Plan for Combating Antibiotic-Resistant Bacteria PACCARB was created to gauge implementation of the National Action Plan, to help optimize government resources and to encourage innovation. The council’s first report commended several departments/agencies on their accomplishments, which included the following:

- Efforts at establishing antibiotic stewardship programs
- Establishment of the CARB Biopharmaceutical Accelerator public-private partnership
- Launching of the Defense Department’s Multidrug-Resistant Organism Repository and Surveillance Network, and
- The FDA’s final ruling of the Veterinary Feed Directive

At the same time, PACCARB emphasized the need for additional work on: 1) advancing the One Health approach; 2) appointing a cross-agency federal champion for oversight; 3) increasing federal response coordination; 4) improving resource allocation; and 5) promoting economic incentives for new tools in diagnosis, prevention and therapy.

**PATH Act endorsed for passage in U.S. Senate**

In early April, the U.S. Senate HELP Committee (Health Education Labor and Pensions) endorsed the Promise for Antibiotics and Therapeutics for Health (PATH Act) (S. 185) during its final mark-up session. The PATH Act is designed to speed the research and development of urgently needed new antibiotics for smaller groups of critically ill patients with life-threatening infections. The Committee, chaired by Lamar Alexander, is still faced with funding issues. “I’m confident that working together we will figure out how to get this bill, along with some funding for the NIH, to the floor,” noted Michael F. Bennet (D-Colo), who co-introduced the bill with Orrin Hatch (R-Utah) in Dec, 2014.

**Discharged patients pose infection threat via contaminated hands**

Hand-washing is not currently a routine practice among the patient population of acute care facilities. In a surveillance study (JAMA Internal Medicine, Mar 14) of six post-acute care facilities in Detroit and SE Michigan, University of Michigan researchers examined the hands of senior patients for MRSA, vancomycin-resistant enterococcus and antibiotic-resistant gram-negative bacilli. Nearly 25% of patients carried one of the pathogens at time of admission, and 34.2% were colonized on follow-up testing—indicating additional acquisition in the post-acute care facility (rehab and nursing homes). Colonization persisted in two-thirds of the carriers up through time of discharge. The data indicate a high probability for pathogen transmission to follow-up facilities and a failure to address one avenue of transmission that could be mitigated by simple patient handwashing interventions.

**Evidence mounts against common household antibacterials**

In September, the U.S. FDA will announce whether the makers of household antibacterial soaps, i.e., triclosan- and triclocarban-containing household cleansers have fulfilled their obligation to prove that these products are superior to regular soaps in keeping people healthy and germ-free.

The chemicals are hypothesized to contribute to the problem of antibiotic-resistant bacteria. While the data are sometimes contradictory and unclear, new evidence of other negative attributes is accumulating. The compounds have appeared in body fluids, most recently in nasal secretions, and have been found to render Staphylococcus bacteria “stickier,” making it more difficult for rats to resist staph infections. In studying zebrafish, researchers have found data suggesting that triclosan exposure
direction, joined most recently by the sandwich chain Subway, which announced the sale of its first antibiotic-free chicken sandwich in early March, and which intends to become entirely antibiotic free by the year 2025.

On the U.S. homefront, a group funded by 62,000 pig farmers—The Pork Checkoff—is supporting a three-pronged stewardship effort which includes research, farmer education and outreach to stakeholders and consumers.

Meanwhile, the call for a reduction in antibiotic use has been reinforced by Kerry McCarthy, Britain’s Shadow Secretary of State for Environment, Food and Rural Affairs. “We need strong international action to prevent antibiotics being given to animals who do not need them, alongside parallel efforts to reduce their use in human medicine,” she said. A few weeks back, the Members of the European Parliament voted in favor of amendments to ban routine preventive use, including group treatments where no disease had been diagnosed in any animal. McCarthy noted, “It is now up to the Council of Ministers and the EU Commission to support this European Parliament vote and for the UK government to take a lead in these discussions.”

Farm antibiotic use remains worrisome in India

While some countries are making strides towards removing growth-promoting antibiotics from food animals, nonetheless, it is estimated that global use will actually increase 67% in the next 20 years as developing countries expand their livestock production to meet the growing demands for animal protein. Of particular concern is India, the largest global consumer of antibiotics, where antibiotic use in livestock is still unregulated. According to a Bloomberg News investigation, farmers are reportedly using cocktails of nine different antibiotics for both infection prevention in young chicks and for general hygiene and animal shed disinfection between flock rearings. Among these are five drugs labelled “critically important” for human infection treatment. The study prompted a Bloomberg editorial which suggested a tax on animal antibiotics in order to incentivize farmers to alter their animal husbandry practices to avoid antibiotics, to raise revenue to permit government

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profundely affects the diversity and community structure of the gut microbiome. More recently, triclocarban—an antimicrobial ingredient of bar soaps—was found in the rat offspring of their exposed mothers, both of which exhibited altered microbiomes. Moreover, the chemicals, when excreted or flushed into the environment, have accumulated in wastewater treatment plants, altering microbial communities and their ability to decompose sewage. Patrick MacNamara’s research team at Marquette University in Milwaukee has reported a spike in bacterial production of the mexB-encoded efflux pump – the same pump which exports common antibiotics. Thus, MexB-carriers have been found resistant to both antibacterials and antibiotics and can leach into the environment, causing further impacts on wildlife, and potentially on humans.

Visit Wellness Wednesday’s “All Sides” (WOSU Radio, April 20, 2016) for a recent interview with Drs. Patrick MacNamara and Stuart Levy on the impacts of antibacterial soaps.

Chlorhexidine tolerance found in hospital isolates

Chlorhexidine is a commonly used hospital antiseptic employed in body washes, oral rinses and central line care for decreasing the burden of nosocomial infection, particularly *S. aureus*, in hospitalized patients. Concern has arisen over the possible emergence of the *S. aureus* genes *qacA*, *qacB* and *smr* which encode multidrug efflux pumps for chlorhexidine and other antiseptics. In an ongoing surveillance study, McNeill and colleagues have reported that 45% of nosocomial *S. aureus* carried one or more of these genes and that such strains were highly associated with reduced susceptibility to systemic antimicrobial agents.

Developments edge towards greater control of farm antibiotics

In the US and UK, a sizable group of investors called ‘Farm Animal Investment Risk and Return’ is pressing large restaurant chains for a comprehensive strategy, including clear timelines, to reduce the use of critical human antibiotics among their meat suppliers. They argue that failure to do so may threaten their investments and pose risk to their reputations. Several large fast-food chains have already taken steps in that direction, joined most recently by the sandwich chain Subway, which announced the sale of its first antibiotic-free chicken sandwich in early March, and which intends to become entirely antibiotic free by the year 2025.
action, and ultimately, to reduce antibiotic use and resistant infections.

India’s 2011 National Policy for Containment of Antimicrobial Resistance called for a ban on nontherapeutic and OTC sales, as well as rules for livestock use, but was met with such protest that it was abandoned. While a sudden ban would “collapse the current production system overnight”, it is still estimated that such legislation will take effect within the next five years. In the meantime, farmers are requesting more powerful remedies as their current drugs show signs of failure.

Multi-drug resistance is the new “norm” on swine farms

A Michigan State University research team, led by James Tiedje has studied large-scale swine farms (concentrated animal feeding operations or CAFOs) in both China and the U.S. Their report, published in mBio (Vol. 7:2) describes a new “norm”: an abundance of multi-drug resistant bacteria in pigs fed antibiotics for growth promotion and disease prevention. Parallel trends were noted in “partner genes”, i.e., resistance genes and the genetic elements that mobilize them, tended to increase or to decrease together. The partner genes often confer resistance to antibiotics not fed to the animals, meaning that dosing with a single antibiotic leads to the rise of bacterial resistance to multiple drugs.

Sewage treatment plants harbor superbugs

A growing number of reports indicate that wastewater treatment plants are not eliminating antibiotic resistant pathogens and are actually allowing them to propagate and grow stronger. U.S. EPA scientists have recently reported finding highly resistant carbapenem-resistant Enterobacteriaceae (CRE) in the pretreated wastewater of a Los Angeles sewage plant that pumps its treated waste into the Pacific ocean—five miles offshore and 190 feet below the surface. The CRE matched that found in previous outbreaks in a California university and two area hospitals.

Millions of gallons of raw hospital sewage enter treatment plants daily. Dr. James McKinnell, infectious disease expert at the Los Angeles Biomedical Research Institute said, “The idea of CRE flowing down our sewer pipes gets me nervous.
We should be testing our runoff.”

But little is known about the quantities of pathogens actually entering the Pacific or whether these effluents are returning to impact the shoreline. Some 8% of patients sick with CRE have not previously visited a health care facility, causing some concern for generally healthy people such as swimmers and surfers at local beaches. Even waste that was treated with chlorine has been found to still harbor the NDM-1 superbug (Yi Luo et al. 2013).

Besides carrying dangerous pathogens from patient waste, hospital sludge also contains high levels of antibiotic residues that exert selective pressure, resulting in additional resistance gene transfer.

For more on this topic, see APUA’s focus article by Edo McGowan on wastewater treatment here (APUA Newsletter Vol. 32:2) and this new article by Hocquet et al. (J. Hosp Infect, Feb 2016)

New dashboard app created for antimicrobial resistant pathogens

A team of researchers led by S. A. Hasham at Michigan State University has developed a new, freely available application for the gathering and geospatial mapping of antibiotic resistance genes from environmental and clinical settings. The Antibiotic Resistance (AR) Dashboard contains two key tools: an antibiogram dashboard, and a dashboard for geographically linking resistance genes and resistant bacterial hosts.

The database is designed to receive and integrate multiple data sets which can be used for offline analysis. The authors invite interested users to download a beta version and submit antibiotic sustainability data and to provide feedback on utility. The authors envision multiple functions, including identification of regional or global “hotspots”, tracking and linking spread, and differentiating natural resistances from those generated by humans and animals among others.

Simple strategies found to reduce antibiotic overprescription

Using insights gained from behavioral economics and social psychology, a team of researchers from the University of California and Harvard medical School have reported simple and inexpensive strategies for successfully reducing antibiotic
prescription abuse. The study, reported in JAMA Internal Medicine (Vol 315:6), focused on acute respiratory infections not requiring antibiotics. In one approach—a “peer comparison” tactic—doctors received a monthly e-mail informing them of their performance stats and comparing them to those of their peers (i.e., “top performer” vs. “not a top performer”). With this approach, improper antibiotic prescribing dropped 81% (from 19.9% to 5.2%). A second approach prompted physicians to supply an “antibiotic justification note” in patient records whenever prescribing was clearly not indicated. Besides requiring an extra step, the note, which was also visible to others, introduced social accountability. This method resulted in a 77% reduction in over-prescribing—from 23.2% down to 5.2%.

**MRSA Updates**

**Tarocins create “Achilles heel” in MRSA**

A new class of drugs called tarocins (tarocin A and tarocin B) acts in partnership (i.e. as an adjuvant) with current antibiotics to interfere with a fundamental cell wall building block—wall teichoic acid (WTA). WTA is instrumental in promoting bacterial colonization in gram-positive bacteria. The findings, reported by Merck Research scientists Christopher Tan and colleagues in Science Translational Medicine, represent a novel approach towards new drug development since the tarocins do not kill the cells directly, but rather improve the activity of existing drugs. To date, the compounds have been used successfully (in conjunction with penicillin family drugs) to kill MRSA (methicillin-resistant *Staphylococcus*) and MRSE (methicillin-resistant *Staphylococcus epidermidis*), both in vitro and in mice with minimal toxicity. Tests in humans are pending.

**Ultra-short antimicrobial peptide shows promise as MRSA weapon**

A team of researchers at the A*STAR Experimental Therapeutics Centre in Singapore has designed and synthesized a promising, ultra-short antimicrobial peptide for treatment of MRSA skin infections. Peptides disrupt cellular membranes very quickly, thereby diminishing their potential to develop resistance through mutation. To date, the shortest antimicrobial peptide in clinical trials is Omiganan, which consists of 12 amino acids. The A*STAR peptide is equally effective, but has just 4 amino acids and only two different amino acid types, which will greatly reduce the cost and time of the manufacturing process.

**Copper may help reduce environmental contamination**

Dr. Sarah Warnes and scientists at the University of Southampton have been using simulated fingertip contamination of surfaces to test surface decontamination of MRSA. They found that copper and its alloys can damage bacterial respiration and DNA—resulting in much more rapid cell breakdown and death than occurs on traditional stainless steel surfaces. The findings show potential for controlling the epidemic spread of MRSA in health-care facilities.

**Rapid Diagnostics in the News**

**FDA clears Cepheid test for carbapenem resistance genes**

In March, Xpert® Carba-R became the first FDA-cleared test for the detection and differentiation of carbapenemase genes. The new diagnostic is a qualitative, rapid (under 30 min) *in vitro* test for detecting distinct families of the most common carbapenem resistance genes: KPC, NDM VIM, OXA-48 IMP, and now covering OXA-181 & OXA-232.

The test overcomes the numerous deficits posed by conventional laboratory methodologies for identification of these difficult-to-characterize mechanisms. The release roughly coincided with the CDC’s Vital Signs Report: Preventing antibiotic resistant infections in Hospitals—US 2014, which noted the urgent threat of the carbapenemase-resistant *Enterobacteriaceae*. The test became available in the U.S. in March 2016 and runs on the GeneXpert® System platform.

**MALDI-TOF meets VRE**

University of Washington researchers have devised a more rapid method for identifying vancomycin-resistant strains of MRSA, in particular, the intermediate form (VISA), and the heterogeneous form (hVISA), in which only a fraction of the organisms may be resistant (e.g., one in a million cells). The test uses a mass-spectrometry-based method called MALDI-TOF and takes a broad proteomic profiling approach. The method is 100% accurate for VISA, 76% accurate for hVISA and 89% accurate for susceptible strains.
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 around the globe, 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.
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