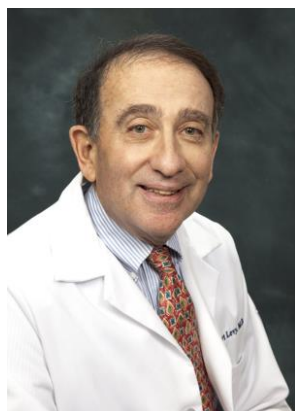


APUA HIGHLIGHTS – FALL 2018

APUA NEWS



APUA President Stuart B. Levy announces retirement from Tufts

Stuart B. Levy, MD, co-founder and president of APUA for 37 years, has recently announced his retirement from Tufts University School of Medicine in Boston. During his more than four decades at Tufts, Dr. Levy has led a paradigm shift in how we view antibiotic use and stewardship. In his work on mechanisms of antibiotic resistance and spread of resistance determinants among microbes, his voice was among the first of those that warned of the dangers of antibiotic overuse and the emergence of drug resistance. In 1981, he co-founded *The Alliance for the Prudent Use of Antibiotics*, the first, and for a long time, the only, organization of its kind committed solely to antibiotic preservation. Under his leadership, the organization expanded its influence to include chapters and members in many countries around the globe. Through this vehicle, as well as his 1992 book, *The Antibiotic Paradox: How Miracle Drugs are Destroying the Miracle*, the world became better informed of the perils of antibiotic misuse. With Levy's continued call for removing the growth-promoting use of antibiotics in food animals, the U.S. Food and Drug Administration ultimately issued guidelines that called for more judicious use of these drugs in animal husbandry.

As a Distinguished Professor in the Department of Microbiology and Molecular Biology at Tufts, Dr. Levy leaves behind a legacy of outstanding accomplishments that emanated from the Center for Adaptation Genetics and Drug Resistance, which he founded in 1992.

We are pleased to share that the September issue of *National Geographic* features an article, [*The Surprising Way Drugs Become Useless Against Bacteria*](#), which describes how Dr. Levy received his early inspiration to embark upon his pursuit of unravelling some of the mysteries of antimicrobial resistance.

The staff and board of APUA are deeply grateful for the vision, energy and dedicated leadership that Dr. Levy has exhibited over these many years and we wish him the very best in his well-deserved retirement.

APUA signs onto REVAMP Act of 2018

APUA has joined multiple healthcare-associated groups in lending its support to [House Bill HR 6294](#), introduced by Rep Shimkus (R-IL) on June 28, 2018. The letter, directed to the Committee on Energy & Commerce, expressed support for [REVAMP: Re-Valuing Antimicrobial Products Act of 2018](#). It expressed the signees' deep concern for the serious threat of antimicrobial resistance, the insufficient number of defenses to combat the threat, and the great concern over the potential for weaponizing antibiotic-resistant pathogens for bioterrorism. The lack of sufficient resources to face these threats is described as an "impending crisis that requires immediate action to mitigate." As there are currently only eight truly innovative products in development, the letter outlined the need for incentives that will insure the development of resources to protect the country adequately. It supports the REVAMP legislation and encourages its inclusion in the reauthorization of the Pandemic and All-Hazards Preparedness Act (PAHPA), aimed at protecting Americans from antimicrobial resistance and weaponized pathogens. The REVAMP act outlines the criteria for establishing a list of "critical need antimicrobial priorities" and provides for an award of 12 additional months of market exclusivity to a drug designated as a "priority antimicrobial product."

Gordon William Grundy, MD (1944 – 2018)



It is with deep regret that APUA shares the news of the recent passing of Dr. Gordon Grundy, who served 12 years as a valued member of the APUA's board of directors. Dr. Grundy came to APUA as Regional Medical Director for the Northeast United States at Aetna where he assumed a final career of investigating fraud and abuse in healthcare. His leadership, enthusiasm, and generosity with advice and assistance to the APUA staff were of immeasurable aid, and demonstrated his unswerving commitment to APUA's mission of preserving the power of antibiotics. Those who knew him well recall his great passion for books, in particular, his prized library of nearly 1000 biographies.

APUA offers its deepest condolences to the Grundy family on their loss.

ANTIBIOTIC RESISTANCE IN THE NEWS

DEVELOPMENTS IN POLICY

New U.S. bill introduced to increase oversight of antibiotic use in animals

In June, U.S. democratic senators Warren, Gillibrand, Feinstein and Blumenthal introduced into the legislature a new bill known as the [Strengthening Antibiotic Oversight Act \(S3099\)](#). The bill is designed to give the FDA the ability to collect better data on animal usage of antibiotics and also ensure that medically important antibiotics are used sparingly. The bill would require FDA review of drug durations and allow withdrawal of approvals for durations that are unjustified. It will require that animal drug user fees be used to collect data on farm antibiotic use.

Canada urges action, federal leadership, for AMR problem

In 2017, APUA director Jane Kramer testified before the House Commons Standing Committee on Health regarding the problem of antimicrobial resistance (AMR). Following two years of study that heard testimony from multiple witnesses, the Canadian Parliament has issued a [new report](#) calling for accelerated development of a plan to address the country's AMR problem, including more federal leadership and coordination. While Canada has made significant efforts to tackle AMR, it states that needs to be done in terms of surveillance of AMR and antimicrobial use.

Tripartite memorandum steps up 'One Health' agenda

Subsequent to WHO's November 2017 issue of guidelines that recommended the cessation of medically important antibiotics for growth promotion and disease prevention in healthy animals, leading global policy makers have now called for more responsible use of antibiotics in food animals.

In a joint, high-priority AMR meeting of the FAO (Food and Agriculture Organization), WHO and OIE (World Organization for Animal Health), held in May 2018, FAO Director-General José Graziano da Silva called for the immediate phase-out of antibiotics for growth promotion use in livestock and aquaculture as well as limitations on its use for disease prevention. Food-producing animals are the target of up to 80% of all antibiotic sales, and the FAO estimates that more than 60% of current and emerging human pathogens actually originate in animals.

The Tripartite Partnership issued a [Memorandum of Understanding](#) in which it agreed to not only strengthen its longtime collaboration on antimicrobial resistance (AMR), but to increase efforts on improving disease-forecasting capacities. The three agencies will continue working to implement the Global Action Plan on AMR, which only 89 countries currently have in place. Recent successes of the collaboration are: the launch of an AMR national action plan in Ghana; assistance in boosting Cambodia's surveillance capacity; and aiding Vietnam in incorporating antimicrobial stewardship into national law. Other joint activities include assessing risk, and preparing to detect and respond swiftly to emerging zoonotic disease.

New guidance released for building health worker knowledge and hospital stewardship programs

WHO has released a 28-page document titled [WHO Competence Framework for Health Workers' Education and Training on Antimicrobial Resistance](#)—aimed at improving healthcare worker's education and training on antimicrobial resistance (AMR). The document helps meet the first objective of WHO's Global Action Plan on AMR, released in 2015. The guidance is presented in a series of tables that outline the knowledge, skills and attitudes needed by four categories of health worker for four "domain areas" consisting of: 1) foundations that build awareness of antimicrobial resistance; 2) appropriate use of antimicrobial agents; 3) infection prevention and control and 4) diagnostic stewardship and surveillance."

Meanwhile, an international team of experts has published core elements and a checklist for establishing the first [universally relevant standards](#) for hospital antimicrobial stewardship programs (ASP)—ones that cover both resource-rich and resource-limited institutions. The panel utilized literature and website searches to compile seven minimal core elements of an APS and also 29 checklist- questions to determine compliance with the core items. The core elements resemble those laid out by the U.S. CDC in 2015: leadership commitment, accountability, drug expertise, action, tracking, reporting, and education. Testing for feasibility in a range of clinical settings is still pending.

EU coalition (EU-JAMRA) seeks national action plans for member states

The EU has announced a new [EU Joint Action on Antimicrobial Resistance \(AMR\) & Health Care Associated Infections, called EU-JAMRAI](#). The major effort of the new coalition is to ensure that all EU member states have solid national action plans. This will be accomplished through 9 work packages (WPs). Work packages 1, 2, 3, and 8 will coordinate projects, evaluate progress and disseminate and communicate results. WPs 4 and 5 will implement One Health national strategies and national action plans. WP6 will work on creating and implementing policies to

prevent healthcare-associated infections; WP7 will develop a database of current guidelines for both animal and human antibiotic stewardship; WP9, led by France and Norway, will be investigating “pull incentives” for development of new antibiotics in Europe.

New guidelines issued for *C. difficile* management

A joint panel of experts from the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) has updated the 2010 [guidelines](#) for the management of *C. difficile*, as outlined in the March 2018 issue of Clinical Infectious Diseases. The guidelines update recommendations regarding epidemiology, diagnosis, treatment, infection prevention, and environmental management. Specifically, they reflect the evolving controversy over optimal diagnostic methodologies, and contain significant changes in infection management, as well as inclusion of recommendations for children. For the first time in almost three decades, metronidazole is no longer recommended as first-line therapy in adults. It is anticipated that pharmacists can play a pivotal role in ensuring optimal therapy for patients who may be receiving outdated treatment.

FDA to implement five-year blueprint for antimicrobial stewardship in farm animals

U.S. Food & Drug commissioner, Scott Gottlieb, MD, has announced the release of a 5-year blueprint ([Supporting Antimicrobial Stewardship in Veterinary Settings](#)) for furthering the FDA’s efforts established by its Guidance for Industry #213. That Guidance called for elimination of growth-promoting use of antimicrobials and for veterinary oversight of these drugs. The new 5-year plan will advance stewardship efforts by establishing appropriate durations for medically important antimicrobials—many of which currently lack such information on their labels. The plan also focuses on better monitoring of drug use and antibiotic resistance, improved collection and sharing of data, and increased transparency for the public.

Innovet-AMR: a new partnership seeks alternatives in livestock, aquaculture

Canada and the UK have announced a new initiative to combat antimicrobial resistance in low and middle income countries (LMICs). The four-year initiative, *Innovative Veterinary Solutions for Antimicrobial Resistance* ([Innovet-AMR](#)) is funded with \$22.1M (USD) and will support research into innovative veterinary solutions, including new animal vaccines to reduce antimicrobial use in livestock and aquaculture.

Ghana launches antimicrobial resistance policy

The platform of WHO's 2030 Sustainable Development Goals (SDG3) demands that all countries "ensure healthy lives and the promotion of well-being for all at all ages." <http://www.who.int/sdg/targets/en/> As a co-chair of this UN group, Ghana president, Nana Addo Dankwa Akufo-Addo, has recognized the grave threat posed by antimicrobial resistance and instituted a [National Action Plan](#) for antimicrobial resistance, together with a national policy document. He has urged Ghanaians to join in efforts in implementing the antimicrobial resistance plan and charged industry with the task of bringing forth new antimicrobials, vaccines and diagnostics. He added, "We are mobilizing domestic resources to deal with this menace, a mobilization which is an integral part of our vision for creating a Ghana Beyond Aid."

Novartis abandons antimicrobial development

The Switzerland-based pharmaceutical giant, Novartis, declared in July, 2018, that it is no longer pursuing development of new antivirals and antibacterials—thereby abandoning its 32 antimicrobial projects in the pipeline, seven of which were in clinical stage development. As profit margins for antimicrobials have declined, Novartis has joined the ranks of Allergan, Sanofi, and AstraZeneca, who have also withdrawn from antimicrobial research. Executive director Jenn Leeds offered the following explanation: "The industry faces an impasse in bringing new antibacterial medicines to patients. The commercial model for anti-infectives is critically challenged, and we (like many others) are left questioning whether large pharma can sustainably support the required, significant infrastructure needed to discover, develop, and commercialize anti-infectives." She suggests that the gap can be filled by academic research, coupled with small- and medium sized enterprises (SMEs) that can "help with generation and validation of approaches by rigorous preclinical testing and testing novel approaches clinically." The company intends to continue with discussions to produce, market, and sell antibiotics developed by SMEs.

ADVANCES IN ANTIMICROBIAL DEVELOPMENT

Moving beyond antibiotics: the prospects for bacteriophage therapy

The therapeutic potential of bacterial phages in treating infection has been recognized for over 100 years, but no products of this kind are commercially available in the U.S. Prior to the advent of sulfa drugs and penicillin in the early 1900s, phages were actually available in U.S. drugstores and were utilized for a variety of ailments. While they fell out of favor following the

enormous successes of the broad-spectrum antibiotics, fortunately, clinical use and research on phage therapy persisted in Eastern nations, particularly Georgia and Poland. However, they remained largely inaccessible and opaque to Western medicine until the emergence of multidrug resistant (MDR) bacteria that failed all available antibiotics. The specificity of bacterial phages, i.e., their ability to target just one bacterial species has hindered their development in the West. Consequently, there are huge knowledge gaps about dosage, toxicity efficacy and methods of delivery. Because of their unique characteristics, they do not fit neatly in the U.S. regulatory framework. Unlike single molecule antibiotics, they must be delivered as phage “cocktails” in order to address rapidly evolving bacteria that may develop resistance.

The dire circumstances presented by extreme MDR infections have prompted desperate efforts to save the lives of three U.S. citizens succumbing to these infections: one with *Acinetobacter baumannii* (pancreatic); a second with *Pseudomonas aeruginosa* (prosthetic graft of the aorta); the third—*Burkholderia cepacia* in a cystic fibrosis patient. While last-ditch efforts to quickly assemble an effective phage cocktail proved successful for the first two patients, the third did not. This latter failure, in a 25-year-old woman, prompted a call for a phage directory (<https://phage.directory/>) —a searchable catalog of available phages and their bacterial targets that have been studied. This one step will facilitate identification, and hopefully, acquisition of ideal phages for critically ill patients. Still, clinical trials, such as the one being conducted in European burn patients (PhagoBurn), are crucial for eliminating the many hurdles confronting phage therapy and moving it from a last-ditch measure to a commercialized, routine, therapeutic alternative to present-day antibiotics.

Central to this effort in the U.S. is the launching of a clinical center founded by researchers at the University of California San Diego, funded with \$1.2 million and staffed with 16 researchers and clinicians to start. The new [Center for Innovative Phage Applications and Therapeutics \(IPATH\)](#) is set to become a “game changer” for phage therapy in the U.S. and aims to answer important questions surrounding dosage and route of administration, etc. Through fast-tracked USDA approval, 6 patients have been successfully cleared of serious MDR infections. Unlike the current European PhagoBurn trials, which frequently consist of multispecies infections, IPATH will not manufacture phage, but will focus on single species infections to devise and seek approval for a library of about 100 phages for each bacterial species. The group will collaborate on outside, multicenter trials with chronic MDR infections in organ transplants, implanted devices and cystic fibrosis.

Roundworms help identify antibacterial properties of retinoids

Utilizing roundworms infected with MRSA as a screening tool, Rhode Island scientists have conducted a massive [evaluation](#) of 82,000 lab-made molecules, and found two compounds that

show promise as antibiotics. These were identified as retinoids—compounds that are chemically similar to vitamin A and were previously used in the 1960s for treatment of acne and cancer.

Retinoids disrupt bacterial membrane lipid bilayers, making them “leaky”. Although they are not active against gram-negative bacteria, importantly, retinoids clear both normal and dormant cells (“persisters”) of MRSA. Moreover, they were even more potent when combined with gentamicin. One of the retinoids has been modified to reduce toxicity and used effectively to dramatically reduce MRSA in mice, without causing any apparent side effects. No resistant mutants were found following exposure to high retinoid concentrations; and long-term exposure (100 days) to low-level concentrations yielded only two-fold higher resistance (compared with a 256-fold increase with ciprofloxacin). Human trials are still several years away.

Teixobactin development takes ‘quantum leap’

The novel, groundbreaking antibiotic, [teixobactin](#), which was originally derived from soil bacteria in 2015, is now one step closer to a commercially viable drug. A University of Lincoln team (UK) has [developed a library of synthetic versions](#) by replacing key amino acids in the molecular structure to facilitate production. After demonstrating that these simplified, synthetic versions were highly potent against MRSA and vancomycin-resistant enterococcus (VRE) in vitro, collaborators in Singapore tested efficacy in mice. The new drug not only cleared MRSA infection, but minimized infection severity. While this success represents a “quantum jump” in progress, teixobactin still remains at least 6-10 years away from clinical use in humans.

Synthetic polymers as antibiotics

Synthetic polymers known as polycarbonates have demonstrated efficacy in killing gram-positive bacteria such as MRSA by causing massive disruption of the bacterial membrane. But using this vehicle against gram-negatives is problematic because massive membrane disruption in this bacterial type can release toxins that result in septic shock. This challenge has been tackled by IBM- and Singapore-based collaborators by using polycarbonates as a platform for constructing molecules with a specific structure and function. The research team [reported](#) that adding guanidinium groups to the polycarbonate platform left the membrane intact, allowing transport across it into the cell cytosol, killing the cell from within and biodegrading thereafter. The novel materials proved effective both in vitro, and in vivo against MRSA in mouse models, and against the gram-negatives—*E. coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*—with no toxic side effects. Importantly, when *Acinetobacter baumannii* was repeatedly exposed to 30 passages of sub-lethal doses, no resistance was

found—in contrast to the imipenem control, which developed resistance after eight exposures. The team is looking into further refinement, as well as the mechanisms that circumvent the development of resistance.

Soil-dwelling nematodes yield novel antimicrobial

Collaboration between the University of Illinois and a Lyons, France biotechnology company has yielded a new class of naturally produced antibiotic called odorhabdins (ODLs). The compounds were [isolated](#) from symbiotic bacteria (*Xenorhabdus nematophila*) that inhabit soil-dwelling nematode worms and help protect them from competing bacteria.

Like other antibiotics, the ODLs work by targeting the bacterial ribosome—but at a different ribosomal site than reported previously. When bound to the ribosome, ODLs cause it to make reading errors when creating new proteins, resulting in bacterial cell death. Researchers engineered more potent derivatives from the original compound and tested them in mice infected with pathogens. ODLs were effective in treating not only gram-negative and gram-positive pathogens, but importantly, carbapenem-resistant *Enterobacteriaceae*, which can contribute to the death of up to 50% of infected patients. The unique qualities of the ODLs indicate that they possess the potential to treat unresponsive infections.

Turning MRSA on itself

MRSA is genetically hardwired to absorb fat and use it as a shield against antibiotics that target fatty acid synthesis. This feature has provided the pathogen with an evolutionary advantage. It is hypothesized that the fat source in humans is blood-based lipids, which MRSA steals and incorporates into its own membrane.

Using mass spectrometry, researchers at Michigan State University have [observed](#) for the first time how MRSA secretes lipases that free fatty acids from human LDL cholesterol. The observation opens the possibility for finding a means of preventing this access.

Using computer algorithms to develop antibiotics

Scientists at MIT and the University of Brasilia have succeeded in utilizing the power of computer-based algorithms to derive candidate antibiotics that could combat serious gram-negative infections. The team approached plant microbial peptides, which clearly have potential as potent antimicrobials, but have evaded development into useful drugs for four decades—due either to their length, post-translational modifications, or high-dose requirements. The computational approach to exploring natural products is a ‘first’ for

replacing the laborious and time-consuming process of synthesizing, screening, and ultimately testing hundreds of new variants for efficacy against different bacterial pathogens. Utilizing principles from Darwin's theory of natural selection, the algorithm starts with any peptide sequence, generates thousands of variant compounds and tests them for specific desired traits. Consequently, only a very small fraction of candidates requires subsequent testing with traditional methods.

Starting with a peptide (Pg-AMP1) from the seeds of a guava plant, which shows only weak antibacterial activity, scientists directed the algorithm to develop sequences that would facilitate penetration of bacterial membranes, alpha helix formation, and hydrophobicity. Their top candidate, [guavanin-2](#), proved especially potent against gram-negative bacteria and successfully cleared mice of a *Pseudomonas aeruginosa* skin infection.

Based on this success, the team now aims to seek other potent antimicrobial peptides and to develop guavanin-2 for possible use in humans, which could be the first such application.

ADVANCES IN ANTIMICROBIAL STEWARDSHIP

Antibiotic supply chain “fragile” – deepens resistance crisis

A [white paper](#) released by the Dutch non-profit, *Access to Medicine*, describes current shortages in antibiotics that fuel the antibiotic resistance crisis. Matching the correct antibiotics with the right patients at the right time is crucial to successful infection treatment. Inadequate supply chains can result in several undesirable outcomes: use of lower doses, use of less appropriate medications, delays in treatment and higher prices, which encourage poorer quality drugs. All these factors are known to increase risk of antibiotic resistance. Diminished supplies are reportedly due to a number of factors: too few manufacturers (which can destabilize supplies during a malfunction, e.g., the Chinese factory explosion of raw starter materials for piperacillin-tazobactam production); an unstable economic model in which profits are unpredictable; and lack of a global procurement system.

In 2015, 39 countries, including India, Australia and the US, reported shortages of benzathine penicillin G, which blocks maternal–fetal transmission of syphilis. The shortage of the combination drug piperacillin-tazobactam, which is on WHO's essential medicines list, resulted in restriction to severe infections only, and put patients at risk from the side effects of alternative drugs, such as developing *C. difficile* infection. Antibiotic shortages have in some cases shifted usage to last-resort antibiotics.

According to the authors, the “antibiotic supply is patchy, complex and at risk of collapsing.” To others, ongoing shortages “are probably as large a problem as the lack of new antibiotics,” and “predicting global and local shortages will continue to be unpredictable.” Some have suggested the need for greater transparency within the entire supply chain, and recommend a global procurement system with better cooperation between pharmaceutical companies, governments and medical providers.

Lord O’Neill castigates pharma industry and European farmers for inaction

In 2016, the outspoken former British Treasury Minister, Lord O’Neill, completed a published series on the global cost and toll in lives of antimicrobial resistance, concluding that 10 million lives could be at risk annually by mid-century at a global cost of more than £70 trillion (\$92T U.S.)

In a [letter to the Journal of Applied Microbiology](#), he sharply criticized EU member states for their seeming disregard of 10-year-old antibiotic bans on farm use of antimicrobials and urged an outright prohibition on antibiotics of last resort, such as colistin. Adding that it might not be “tough enough”, he also stated, “I am shocked at the endless words that come from the pharma industry about their collective belief in the need to fight AMR, but the lack of concrete initiatives and, more importantly, money...”

To date, the UK and 6 other EU nations have reigned in their antibiotic usage below O’Neill’s recommended limit of 50mg per kilo of meat; however, it is strongly surmised that some of the large volumes of antibiotics consumed by farms in countries such as Italy, Greece and Portugal are being used as growth promoters.

SURVEILLANCE AND EPIDEMIOLOGY

Repeated low-level antibiotic exposure yields high level resistance

Swedish scientists have recently [demonstrated](#) that *Salmonella enterica* serovar Typhimurim, when repeatedly exposed to non-inhibitory amounts of streptomycin, could evolve with high-level resistance. Exposure to one-fourth of the usual inhibitory dosage for 900 generations reduced growth by 3% and resulted in four clones with high-level resistance. Unlike mutations that evolve from lethal exposure, five genetic mutations were found that are not typically associated with resistance. When the five genes were combined, the interaction of the mutations resulted in evolution of a higher than expected resistance: 1000-fold more resistant than the exposure level. The findings suggest a possible underestimation of the actual number of genes associated with antibiotic resistance.

The finding has particular implications for low-level antibiotic use in the environment, especially in animal husbandry and for low-level residues found worldwide found in fresh and wastewater. Since up to 80% of consumed antibiotics are excreted, low concentrations may persist in the environment and contribute to the evolution of antibiotic resistance. The studies are being expanded to other antibiotics and other bacterial species, and also to testing in natural settings outside the laboratory.

More challenging superbugs on the horizon: pan-resistant infections on the rise

In 2016, the U.S. Centers for Disease Control (CDC) established a network of regional, state and city labs called the [Antibiotic Resistance Laboratory Network \(ARLN\)](#) to search for some of the most serious multidrug-resistant pathogens—namely, carbapenem-resistant *Enterobacteriaceae* (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA).

In April 2018, the very first [ARLN data](#) became available and yielded a surprisingly higher than expected number of “unusual” genes described as the “worst of the worst”. From 5,776 multidrug-resistant pathogens tested, one in four contained a mobilizing gene and 221 contained rare, virtually untreatable carbapenemases—ones other than the more common *Klebsiella pneumoniae* carbapenemase (KPC). Moreover, the screening of asymptomatic healthcare workers from hospitals and nursing homes showed that 11% carried one of the five carbapenemase mechanisms of primary concern: imipenemase (IMP), KPC, New Delhi metallo-beta-lactamase (NDM), oxacillinase-48-like carbapenemase (OXA-48), and Verona integron-encoded metallo-beta-lactamase (VIM). In one of 10 hospital patient cases, the organisms were spread to apparently healthy hospital personnel—e.g., doctors and nurses—who became silent carriers and could then infect others. The CDC’s nation-wide AR Lab Network and its Containment Strategy are working aggressively to identify such high-priority threats, since diagnosis and assertive application of containment measures are known to reduce these infections by as much as 76%.

***Salmonella typhi* approaching pan-resistance**

Prior to 2016, only four cases of extensively drug-resistant (XDR) *Salmonella enterica* serovar Typhi, an agent of typhus, had been reported worldwide. The highly contagious bacterium is spread through contaminated water and food supplies. A [major outbreak in Pakistan](#), where it is endemic, began in May 2016 and spread, resulting in 850 cases of typhoid that were unresponsive to ceftriaxone. Clusters of victims were identified around water sources that were potentially contaminated by leaking sewer pipes. [Genetic analysis](#) revealed that the endemic strain, known as H58, had acquired an additional bacterial plasmid carrying high-level resistance genes, making it resistant to five classes of antibiotics. Azithromycin is the only

remaining effective oral antibiotic, indicating that “treatment options for typhoid are running out.” In addition to ramping up hygiene practices, an emergency vaccination campaign is now underway with a newly approved typhoid vaccine.

With antibiotic resistance increasing by 30% each year in Karachi, Pakistan, it is estimated that all typhoid cases will be multidrug resistant by 2020.

Triple threat posed by Klebsiella

Klebsiella pneumoniae is one the six [ESKAPE pathogens](#) that is largely responsible for the most difficult-to-manage hospital-acquired infections. Because of its inherent capacity for acquiring many mobile antibiotic resistance genes (currently estimated in the hundreds) located on large conjugative plasmids, *K. pneumoniae* has been coined the “canary in the coal mine”—making it a prime target for sentinel surveillance of resistance genes that are being trafficked from environmental strains into the clinical arena. Its array of defenses is now posing a dangerous and worrisome threat to successful treatment.

In 2016, hyper-virulent, carbapenem-resistant *K. pneumoniae* resulted in a deadly outbreak in China. Now, researchers at Emory University (Atlanta, Georgia) have [reported](#) finding the first carbapenem-resistant, hyper-mucoviscous strain that demonstrates enhanced virulence and is also heteroresistant to the “last-resort” drug, colistin. “Heteroresistant” signifies that only a fraction of the cell population is colistin resistant, making it harder to detect with standard tests. The hyper virulence is due to excessive capsular mucopolysaccharides, which produce a viscous and stringy coating that can be detected by a simple “string test.” While the reported superbug is not as virulent as the Chinese strain, lead researcher, David Weiss says, “Finding the combination of antibiotic resistance and enhanced virulence from a clinical isolate in the United States is still alarming.”

First “super gonorrhea” appears in England

Public Health England defines a pan-resistant infection as one that is resistant to every antibiotic in the standard antibiotic panel. In 2017, WHO warned of impending, widespread treatment failure in gonorrhea unless new antibiotics become available. Gonorrhea strains resistant to the current treatment regimen (cefixime or ceftriaxone plus azithromycin) surfaced in Japan, France and Spain in 2011-12, but subsequently disappeared. However, in March 2018, officials announced the [first global report](#) of a UK patient (having had a prior Asian sexual contact) who exhibited *Neisseria gonorrhea* bearing high-level resistance to dual antibiotic treatment as well as other antibiotics (“super gonorrhea” or MDRGC). Initial empiric treatment with ceftriaxone, followed by spectinomycin failed to clear the infection, which also exhibited

azithromycin resistance. Doctors then resorted to an intravenous carbapenem (ertapenem) to resolve the infection. MDRGC have subsequently been reported in Australia.

Plasmid transfer found among unrelated hospital bacteria

Carbapenem-resistant *Enterobacteriaceae* (CRE), which commonly include strains of *E. coli* and *Klebsiella pneumoniae* are an urgent public health threat, causing 9000 health-associated infections and 600 deaths annually in the US alone. Plasmid-mediated carbapenem resistance can now be [transferred and found](#) among unrelated bacteria in the U.S. healthcare setting. Whole genome sequencing of 18 patients in a Kentucky hospital outbreak found 3 different beta-lactamase (*bla*) gene variants among CRE strains (18 *Klebsiella* and 2 *E. coli*), indicating a multi-strain outbreak. The implications are that the outbreak may be caused by multiple strains rather than a single one. Control efforts may need to be broadened beyond focus on a single strain. Searches for plasmids that invade multiple bacterial species should include environmental niches, such hospital plumbing—which are known sites for plasmid exchange. According to lead researcher Richard Stanton of the CDC, “This outbreak shows us how drug resistance genes can be shared among otherwise unrelated bacteria co-existing in a patient’s microbial community or in the environment.”

CPE control — a losing battle?

A new [study](#) suggests that more than 50% of carbapenem-resistant *Enterobacteriaceae* (CPE) acquisition events in the hospital are directly or indirectly related to contaminated disposables and sink drains. The intervention study centered around two installations: covers for hospital hoppers (a toilet-like disposal unit) that would reduce aerosolization after flushing; and 2) a heater/vibration device that would both sanitize sink drains and prevent biofilm formation. Measurements of clinical cultures of *Klebsiella pneumoniae* carbapenemase-producers (KPC) and acquisition incidents were followed in an 18-month pre-intervention phase and compared with those in an 18-month post-intervention phase. Prior to the intervention, 75% of hoppers and 80% of sink drains tested positive. In the post intervention period, acquisition of new KPCs dropped by nearly one-half and positive clinical cultures fell by two-thirds. Only 5% of culture samples were positive. The “before and after” design of the study does not rule out other factors that may have influenced the outcome, but the results are considered dramatic.

Mechanics of gene transfer visualized for the first time

The uptake of extracellular DNA via bacterial appendages, called pili, has been known for decades. However, until recently the process has never been directly observed. By “painting” DNA fragments and the pili on *Vibrio cholerae* with a special glow dye, researchers at Indiana

University have now [observed](#) the extremely tiny hook-like appendages responsible for the microscopic “harpooning” that pulls DNA into the cell. The cell casts its pili through the cell wall pores and snags a free DNA fragment at its tip. The DNA is then “reeled” back (retracted) through the same tiny pore by folding itself in half. The whole process is highly dependent on the pilus to guide it. According to senior author Ankur Dalia, understanding exactly how pili hook onto the DNA in the transformation process is considered key to determining how the process of bacterial sharing of DNA can be blocked in order to prevent resistance transfer.

Drug users more susceptible to MRSA infection

For drug addicts who also belong to the 2% of the general population that carries MRSA, needle injection carries additional risks. ([MMWR June 2018](#)) This group is 16 times more likely than others to develop severe MRSA illness. CDC experts explain that MRSA on the skin surface can be carried to the subsurface through injection, with the potential for entering the bloodstream and causing organ failure. This form of infection has more than doubled in 5 years—from 4% in 2011 to 9% in 2016.

Microplastics promote gene transfer in aquatic environments

Millions of tons of microplastics from industrial products and degradation of plastic waste are released globally into aquatic systems—estimated to reach 12,000 megatons by 2050. This accumulation of surfaces for potential biofilm formation has led an international team of investigators to [evaluate the increased potential for genetic exchange](#). Using a red-fluorescent *E. coli* donor strain that contains a green-fluorescent, broad-host-range plasmid coding for trimethoprim resistance, the researchers tested their hypothesis by comparing gene exchange in free-living bacteria vs. those forming biofilms on microplastics (polystyrene). They found a 100-fold increase in horizontal gene transfer rates in phylogenetically diverse bacteria grown on microplastics in lake water, and a 1000-fold increase in laboratory water. The findings suggest the potential for distinct global shifts in the ecology of aquatic microbial communities with an associated spread of antimicrobial resistance genes that pose a hazard for human health.

HYGIENE AND INFECTION PREVENTION

Triclosan exposure yields antibiotic-resistant mutants

Residues of the widely used antibacterial, triclosan, have been building in the environment for decades, prompting escalating concerns over its potential for inducing cross-resistance to antibiotics in clinically important bacteria. However, lack of conclusive evidence for the link between the two has largely hindered efforts to reduce triclosan use on a global scale. Using *E.*

coli as a model organism, scientists at the University of Queensland in Australia evaluated exposure to triclosan for 30 days at environmentally relevant concentrations and [found mutations](#) in a number of genes that led to reduced membrane permeability, increased beta-lactamase production and efflux pump activity. The mutations were heritable and resulted in resistance to multiple antibiotics, leading the authors to conclude that triclosan applications in personal care products should be further controlled.

EVENTS AND PUBLICATIONS OF INTEREST

Book: *An Arms Race Against Bacteria*, by W Hall, A McDonnell, & J O'Neill, Harvard University Press, 2018

Videos:

- [Antimicrobials in Agriculture and Food Production: Use, Overuse & Misuse](#), presented by Prof H. Morgan Scott
- [Antibiotic Resistance Explained](#) (Quint Fit) presented by Ramanan Laxminaryan, director CDDEP
- [Keep the Bugs Outta the Club](#) A 30-second clip that won the "Preserve the Power" film contest to help promote understanding of antibiotic resistance; sponsored by the Australian non-profit NPS MedicineWise

Articles: Antimicrobial Stewardship

The following are discussions of the ethical dilemma posed by mass azithromycin use for saving lives of sub-Saharan African children (as reported in [NEJM \(April 2018\)](#))

- [The Catch 2 of mass prescribing antibiotics](#) by Maryn McKenna in WIRED Ideas, 5/10/2018
- [African study on preemptive antibiotics in kids spurs resistance debate](#) by Chris Dall in CIDRAP News, May 2018
- [Giving antibiotics to healthy kids in poor countries: Good idea or bad idea?](#) by Susan Brink in *goats and soda* (npr.org)(Apr-May 2018)

[Antibiotic prescribing and resistance: views from low-and middle-income prescribing and dispensing professionals](#), a report to the WHO from the Antimicrobial Resistance Centre at the London School of Hygiene & Tropical Medicine on data from nine studies undertaken in April to August 2017

[Antimicrobial stewardship through telemedicine and its impact on multidrug resistance](#) by RP Dos Santos et al in *J Telemed Telecare* (2018)

[Nine decades of antibiotics: a story with two endings...](#) Jon Otter blog: Reflections on Infection Prevention and Control (April 26, 2018)

[Fluoroquinolone restriction as an effective antimicrobial stewardship intervention](#) by KC Claeys et al in Curr Infect Dis Rep (2018)

[WHO Competency Framework for Health Workers' Education and Training on Antimicrobial Resistance](#)

[How pharma hides data about farm antibiotic use](#) by Maryn McKenna in WIRED, 6/11/2018

[Answers to common questions about the use of antibiotics in animal agriculture](#) PEW, a 2018 update to reflect newly released FDA sales data.

Articles: Surveillance and Epidemiology in Humans

[The Surprising Way Drugs Become Useless Against Bacteria](#) National Geographic, (September 18, 2018)

[The Rise of Resistance](#) Science -- a special section devoted to 4 review articles on pesticide, antimicrobial, antifungal, and biocide resistance (May 18, Vol 360, 2018)

[Measuring and mapping the global burden of antimicrobial resistance](#) by SI Hay et al in BMC Medicine (2018)

[Global increase and geographic convergence in antibiotic consumption between 2000 and 2015](#) by EY Klein et al in Proc Natl Acad Sci USA (Apr 10, 2018)

[Association between healthcare-associated infection exposure to hospital roommates and previous bed occupants with the same organism](#) by B Cohen et al in Infect Cont Hosp Epidemiol (2018)

[Antibiotic susceptibility and treatment response in bacterial skin infection](#) by JS Lim et al in Ann Dermatol (2018)

[Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey](#) by A Versporten et al in The Lancet Global Health (2018)

[Individual care versus broader public health: a qualitative study of hospital doctor's antibiotic decisions](#) by J Broom et al in Infect Dis and Health (2017)

[Emergence and spread of antibiotic resistance in West Africa: contributing factors and threat assessment](#) by AS Ouedraogo et al Med Sante Trop (2017)

Articles: Surveillance and Epidemiology in Animals & the Environment

[Molecular relatedness of WSBL/AmpC-producing *Escherichia coli* from humans, animals, food and the environment: a pooled analysis](#) by A. Dorado-Garcia et al in J Antimicrob Chemother (2018).

[Antimicrobial drug use in food-producing animals and associated human health risks: what, and how strong, is the evidence?](#) By K Hoelzer et al in BMC Vet Res 13:211 (2017)

[What does the fox say? Monitoring antimicrobial resistance in the environment using wild red foxes as an indicator](#) by SS Mo et al in PLoS One 13, May 25 (2018)

[Small mammals as sentinels of antimicrobial-resistant staphylococci](#) by V Kmet' et al in Folia Microbiol (Praha) (Mar 9, 2018)

Articles: Infection Prevention and Hygiene

[The impact of reducing antibiotics on the transmission of multidrug-resistant organisms.](#) By SL Barnes et al in Infect Cont Hosp Epidemiol (2017)

[Public perception of cleanliness, hygiene and hygiene issues -- a survey of UK and US media coverage 1989 to 2017](#) by S Bloomfield; a new review by The International Forum on Hygiene online (Feb 2018)

[The Economic Value of the Centers for Disease Control and Prevention Carbapenem-resistant *Enterobacteriaceae* Toolkit](#) by SS Huang et al in Infect Cont Hosp Epidemiol (2018)

[Impact of discontinuing contact precautions for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*: an interrupted time series analysis](#) by G Bearman et al in Infect Cont Hosp Epidemiol (2018)

[Preventing healthcare associated gram-negative bacterial bloodstream infections: An improvement resource to help health and social care economies reduce the number of Gram-negative bloodstream infections \(BSIs\) with an initial focus on *Escherichia coli* \(*E.coli*\)](#). A new website by the UK National Health Service

[Magnitude of multidrug-resistant \(MDR\) infections: a peer exchange launched by ContagionR](#), the first four segments of a 16-part discussion, Business Wire, (Mar 2018)

Articles: Diagnostics

[The rapid prediction of carbapenem resistance in patients with *Klebsiella pneumoniae* bacteremia using electronic medical record data](#) by T Sullivan et al in Open Forum Infect Dis, (Apr 28, 2018)

[Impact of real-time notification of *Clostridium difficile* test results and early initiation of effective antimicrobial therapy](#) by CB Polen et al in Amer J Infect Cont (2018)

COMING EVENTS

November 8-9, 2018

[The 6th Annual International C. diff. Awareness Conference and Health EXPO](#) at Philadelphia Airport, PA; up-to-date data to expand on the existing knowledge and raise awareness of the urgency focused on, yet not limited to, a *Clostridium difficile* infection (CDI)—Prevention, Treatments, Research, Environmental Safety, Clinical trials and studies.

November 12-18, 2018

[U.S. Antibiotic Awareness Week](#) (formerly “Get Smart About Antibiotics Week”) is a CDC-sponsored annual one-week observance to raise awareness of the threat of antibiotic resistance and the importance of appropriate prescribing and use.

November 15-16, 2018

[Combating Resistance: Microbes and Vectors](#), 2018 Institut Pasteur International Network Symposium, Institut Pasteur, Paris

February 21-23, 2019

[Antimicrobials 2019](#), Australian Society for Antimicrobials 20th Annual Scientific Meeting, Sydney, Australia

Mar 22-23, 2019

[5th International Conference on Antibiotics](#), Theme: The Antibiotic Resistance Crisis: Causes and Threats, Chicago, IL

March 26-27, 2019

[World Anti-microbial Resistance Congress Europe](#) will focus on developing new antibiotic drugs; AMR challenge: tackling the supply problem, Berlin Germany.

April 13-14, 2019

[15th Annual Global Health & Innovation Conference](#)
Yale University, New Haven, Connecticut

April 13-16, 2019

[ECCMID 2019](#): 29th European Congress of Clinical Microbiology and Infectious Diseases,
Amsterdam, Netherlands

June 3-4, 2019

[6th World Congress and Exhibition on Antibiotics and Antibiotic Resistance](#). Theme: Challenges
and New Concepts in Antibiotics Research, London, UK.

June 20-24, 2019

[ASM Microbe](#), American Society for Microbiology annual meeting, San Francisco, CA

October 2-6, 2019

IDWeek 2019, Washington, DC

June 15-18, 2020

World One Health Congress, Edinburgh, Scotland