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APUA NEWSLETTER

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Looking at the evidence for short-course antibiotic therapy

FEATURE ARTICLE

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APUA AND OTHER ANTIMICROBIAL RESISTANCE NEWS

Northeastern University pharmacy students in Boston once again sponsor their educational 5K *Run From Resistance* with proceeds to benefit APUA. See full story on page 9.

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Gandra

Shorter Duration of Antibiotic Therapy for Bacterial Infections: Is the Evidence Mounting?

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Alvarez-Uria

Antibiotic selection pressure is one of the primary drivers of antibiotic resistance.[1] Antibiotic exposure not only increases resistance in the target bacteria when treating a bacterial infection, but also promotes resistance in non-target bacteria in the intestinal tract and other sites that are not causing the infection.[2] This leads to spreading of resistance genes to other related and unrelated bacteria.[2] Limiting exposure to antibiotics is a key strategy to prevent the escalating problem of antibiotic resistance.[3] A significant proportion of antibiotic use in the community setting is inappropriate—in particular, prescribing antibiotics to treat upper respiratory tract symptoms and acute diarrheal illness, which are predominantly viral in origin.[1,4] However, even in cases of proven bacterial infections, longer than necessary antibiotic courses are unwarranted.

"Short-course antibiotics, where possible, will be beneficial not only to reduce the risk of antibiotic resistance, but also decrease the risk of allergic reactions, C. difficile *infection and patient costs."*

Several clinical trials have established the efficacy of antibiotics by reducing mortality in various bacterial infections.[5] However, these clinical trials did not give serious consideration to precise duration of antibiotic therapy. This could be attributed to lack of incentive to pharmaceutical companies to shorten the duration of antibiotic therapy.[6] Short courses of antibiotics, where possible, will be beneficial, not only to reduce the risk of antibiotic resistance, but also to decrease the risks of allergic reactions and *C. difficile* infection, and to reduce patient costs.[3] To date, there are very limited accounts of bacterial infections where the duration of antibiotic therapy has been established in clinical trials (Table 1).[7-18] Evidence from these studies suggests that there is a substantial opportunity to limit the duration of antibiotic therapy without compromising the clinical outcome. For example, in the case of community-acquired pneumonia among patients who are hospitalized, five days of therapy were shown to be sufficient as long as patients remain afebrile for 48 hours and remained clinically stable.[9] Similarly, in women with community-acquired pyelonephritis, seven days of therapy were as efficacious as fourteen days of therapy.[14] Even among conditions such as pyogenic vertebral osteomyelitis, where duration of therapy might be prolonged up to three months, limiting the duration of therapy to six weeks was found to be successful.[18] In some instances, other interventions can help reduce the duration of the antibiotic therapy. For example, in patients with complicated intra-abdominal infections, the duration of antibiotic therapy after adequate source control (defined as a procedure where infectious foci are eliminated, factors promoting ongoing infection were controlled, and anatomical derangements were corrected) could be shortened to 3-5 days.[12] The outcomes, which included surgical-site infection, recurrent intra-abdominal infection, or death, were similar in the four-day

Table 1. Outcomes with various duration of antibiotic therapy among randomized clinical trials

Study type	Infection	Comparison	Outcome	Comment
RCT[7]	Acute otitis media in young children (6-23 months) treated with amoxicillin-clavulanic acid	5 v/s 10 days	Longer treatment	Clinical failure was more common in the short treatment group and there were no differences in emergence of antimicrobial resistance.
MA[8]	Uncomplicated acute bacterial sinusitis	3-7 days v/s 6-10 days	No difference	Similar clinical success, microbiological efficacy and relapses with both regimens. In a sensitivity analysis, adverse events were less common with the short regimen when comparing 5 vs 10 days.
RCT[9]	Hospitalized patients with community acquired pneumonia	5 days if no fever and clinically stable v/s duration determined by physician	No difference	The median duration was 10 days if the duration was determined by physicians (control group).
MA[10]	Ventilator-associated pneumonia	7-8 days v/s 10-15 days	No difference	No difference in mortality or relapse, although there was a strong trend (odds ratio=1.67) of higher risk of relapse with the short regimen based on the results of one RCT.
MA[11]	Acute exacerbation of chronic bronchitis or COPD	5 days v/s >5 days	No difference	Similar results for clinical and bacteriological cure at early (<25 days) and late follow up. The mean duration of antibiotics in long treatment groups was 8.3 days.
RCT[12]	Complicated intra-abdominal infection after adequate source control	3-5 days v/s 10 days (maximum) or until resolution of fever, leucocytosis and ileus	No difference	The median duration in the short treatment group was 4 days and in the long treatment group was 8 days.
MA[13]	Asymptomatic bacteriuria in pregnant women	Single dose v/s 4-7 days	Longer treatment	Single dose was associated with worse cure rates and low birth-weight of babies.
RCT[14]	Community-acquired acute pyelonephritis in adult women treated with ciprofloxacin 500mg BID	7 v/s 14 days	No difference	Similar clinical and bacteriological outcome 10-14 days after the end of treatment. The study included complicated (patients with diabetes mellitus or abnormalities of the urinary tract) infections. Patients with urinary catheter were excluded.

Table 1 continued

Study type	Infection	Comparison	Outcome	Comment
RCT[15]	Multidrug resistant typhoid fever in children treated with ceftriaxone	7 v/s 14 days	Longer treatment	Initial response was similar, but relapse was more common in the short treatment group.
RCT[16]	Uncomplicated cellulitis treated with levofloxacin 500mg OD	5 v/s 10 days	No difference	Participants who had abscess or no initial clinical improvement were excluded. Many patients had substantial erythema at day 5 but erythema resolved similarly in both groups regardless of the continuation of levofloxacin.
RCT[17]	Uncomplicated skin abscess (diameter <5 cm) after incision and drainage	No antibiotic treatment v/s 10 days	Longer treatment	After 20 days, the cure rate was lower in the no-treatment group if *Staphylococcus aureus* was isolated.
RCT[18]	Vertebral osteomyelitis in adults with microbiological confirmation	6 v/s 12 weeks	No difference	Similar cure rates after one year.

therapy group when compared with other groups with longer duration of therapy.

In contrast to these findings, in certain infections, shorter duration of therapy was found to be inferior. For example, in acute otitis media involving children between 6 and 23 months, five days of amoxicillin-clavulanic acid therapy resulted in more cases of clinical failure when compared to 10 days of therapy.[7] In addition, there was no increase in nasopharyngeal colonization with penicillin non-susceptible pathogens in the 10-day group. Similarly, in another study involving children with multi-drug resistant *Salmonella* Typhi bacteremia, shorter duration of antibiotic therapy with 7 days resulted in bacterial relapse in 14% of patients, whereas no cases of relapse were encountered in patients who received 14 days of therapy.[15] However, including a third group with 10 days of therapy would have been valuable. As enteric fever presents a significant burden in the Indian subcontinent, shortening to four days of therapy could lead to a substantial decrease in overall antibiotic consumption at the population level. These variable findings in the clinical trials further suggest the need for evidence to determine the correct duration of antibiotic therapy for several other bacterial infections.

Shortening the duration of antibiotic therapy without strong evidence will be a difficult task for physicians. A recent international cross-sectional survey by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) involving infection specialists (infectious disease specialists and clinical microbiologists) in 58 countries showed that the majority (64%) of them did not advise the shortest possible duration of antibiotic therapy to prescribers.[18] Efforts to conduct more clinical trials to define duration of antibiotic therapy were made more than a decade ago by professional organizations such as the Infectious Diseases Society of America (IDSA).[6] As support from the pharmaceutical industry will be minimal to conduct these trials, the role of national agencies has been recognized as critical, but progress has been disappointing. On reviewing 24,676 clinical trials classified under the "communicable diseases" category in the Clinicaltrials.gov registry between March 1 and March 31,

Table 2. Clinical trials focused on duration of antibiotic therapy

Infection syndrome	Name of the RCT	Arms	Country	Status
Bacteremia https://ClinicalTrials.gov/show/NCT02261506	Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness: A Pilot RCT (BALANCE)	7 v/s 14 days, ICU patients only	Canada (multi-center)	Completed
https://clinicaltrials.gov/ct2/show/NCT03101072	Antibiotic Durations for Gram-negative Bacteremia (PIRATE)	7 v/s 14days v/s individualized	Switzerland, France (multi-center)	Recruiting
https://ClinicalTrials.gov/show/NCT01737320	Duration of Antibiotics for the treatment of Gram-negative bacilli Bacteremia - a RCT	7 v/s 14 days	Israel, Italy (multi-center)	Recruiting
https://ClinicalTrials.gov/show/NCT02917551	BALANCE on the Wards: A Pilot RCT (BALANCE-Wards)	7 v/s 14 days, non-ICU patients	Canada (single center)	Recruiting
https://ClinicalTrials.gov/show/NCT02400268	Antibiotic Treatment Duration Comparison in Blood Stream Infection Causes by Enterobacteriaceae (SHORTEN)	7 v/s 14 days	Spain (multi-center)	Completed
https://ClinicalTrials.gov/show/NCT03005145	Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness: Randomized Controlled Trial	7 v/s 14 days	Multinational (Australia, Canada, New Zealand, Saudi Arabia)	Recruiting
Bacteriuria (Asymptomatic) https://ClinicalTrials.gov/show/NCT02575495	A RCT of Antibiotic Treatment Duration For Asymptomatic Bacteriuria After Kidney Transplantation	7 v/s 14 days	Thailand (single center)	Completed
Complicated Intra-abdominal Infections https://ClinicalTrials.gov/show/NCT03265834	Antibiotic Duration for Complicated Intra-ABdominal Infection (CABI)	< 10 days v/s 28 days	UK (single center)	Recruiting
Erythema Chronicum Migrans https://ClinicalTrials.gov/show/NCT03337932	Duration of Doxycycline Treatment in Patients With Multiple Erythema Migrans (MEM). A RCT	7 v/s 14 days	Slovenia (single center)	Recruiting
***Helicobacter pylori* Infection** *https://ClinicalTrials.gov/show/NCT01042184*	Efficacy of 10-day and 14-day Sequential Therapy Versus Triple Therapy on the Eradication of *H. pylori*	10 v/s 14 days	Taiwan (single center)	Completed

Table 2 continued on pg. 7

Table 2 continued

Infection syndrome	Name of the RCT	Arms	Country	Status
Neonatal Sepsis https://ClinicalTrials.gov/show/NCT03280147	Comparison of the Efficacy of a 7-day Versus 14-day Course of Intravenous Antibiotics in the Treatment of Uncomplicated Neonatal Bacterial Sepsis: a Randomized Controlled Non-inferiority Trial	7 v/s 14 days	India (multi-center)	Not yet recruiting
Pneumonia, Bacterial https://ClinicalTrials.gov/show/NCT01554657	Five Versus Seven Day Antibiotic Course for the Treatment of Pneumonia in the Intensive Care Unit	5 v/s 7 days	USA (single center)	Completed in 2012
Scrub Typhus https://ClinicalTrials.gov/show/NCT03083197	The Scrub Typhus Antibiotic Resistance Trial (START) Comparing Doxycycline and Azithromycin Treatment Modalities in Areas of Reported Antimicrobial Resistance for Scrub Typhus	7 v/s 3 days	Thailand (multi-center)	Recruiting
Ventilator-Associated Pneumonia https://ClinicalTrials.gov/show/NCT02634411	Impact of the Duration of Antibiotics on Clinical Events in Patients With *Pseudomonas aeruginosa Ventilator-associated Pneumonia*	8 v/s 15 days	France (single center)	Recruiting

2018, we identified only 14 clinical trials in various stages that address the issue of duration of antibiotic therapy for bacterial infections (Table 2). Among these 14 trials, six focused on addressing duration of therapy for gram-negative bacteremia, of which two were completed. Other conditions—each with just one clinical trial—included asymptomatic bacteriuria among kidney transplant patients, complicated intra-abdominal infections, Erythema Chronicum Migrans, *Helicobacter pylori* infection, neonatal sepsis, pneumonia in intensive care unit patients, scrub typhus and ventilator-associated pneumonia.

Although, antibiotic resistance is recognized as a major public health problem globally, efforts to study the precise duration of antibiotic therapy for various bacterial infections seem to be moving at a slow pace. We need to get more serious about generating the evidence needed to rationalize antibiotic courses. Collaborations with national agencies, pharmaceutical companies, other funding agencies and academic research networks are urgently needed to make further progress.

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Upcoming Events

June 7-11, 2018
ASM Microbe, Atlanta, GA

June 13-15, 2018
Association for Professionals in Infection Control and Epidemiology (APIC) Annual Conference. (Minneapolis, MN. USA)

June 22-25, 2018,
5th International One Health Congress, Saskatoon Canada - with special focus on antimicrobial resistance, translational science, and recent advances in the fields of zoonoses and emerging infectious diseases.

July 14-15, 2018
4th World Congress and Exhibition on Antibiotics and Antibiotic Resistance**:** A New Era in Antibiotics Drug Development. (Barcelona, Spain)

July 22-27, 2018
Gordon Research Conference on Drug Resistance: Looking for Common Themes and Solutions in Drug Resistance for Cancer, Infectious Disease and Agriculture (Smithfield, RI, USA)

September 4-7, 2018
ESCMID/ASM Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance (Lisbon, Portugal)

September 24-25
2nd Annual Summit on Antimicrobials and Drug Resistance: Antimicrobes 2018, sponsored by Allied Academies (Montreal, Canada)

October 6-14, 2018
International Course on Antibiotics and Resistance (ICARe)
The Institut Pasteur's course on advanced instruction on antibiotics and resistance that examines cutting-edge approaches for detection of resistance and antibiotic discovery, chemical optimization. (Les Pensieres, Annecy, France)

November 12-18, 2018
U.S. Antibiotic Awareness Week (formerly *Get Smart About Antibiotics Week*): CDC's annual one-week observance to raise awareness of the threat of antibiotic resistance—an international collaboration with European Antibiotic Awareness Day, Australia's Antibiotic Awareness Week, Canada's Antibiotic Awareness Week, and World Antibiotic Awareness Week

November 15-16, 2018
2018 Institut Pasteur International Network Symposium, *Combating resistance: microbes and vectors (*Paris, France)

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APUA in Action

Northeastern University students "Run From Resistance"

For the second consecutive year, APUA is pleased to announce that Northeastern University pharmacy students have chosen APUA as the recipient of their educational 5K fundraiser, *Run From Resistance,* in Boston. An introduction to the April 8 Field Day event was provided by APUA board member Arnold Reinhold, who spoke on the history and mission of APUA. Over 100 runners and ~50 additional attendees participated, raising $1400 for the mission and activities of APUA. In addition to the race, the event included multiple games, informational posters and educational tables, all aimed at raising awareness of antibiotic resistance and the superbug problem. APUA is deeply grateful to the pharmacy students of Northeastern University for their interest in, and commitment to, this increasingly important societal problem.

APUA offers support for STAAR Act; Senator Brown reintroduces legislation

In February 2018, APUA joined multiple stakeholder organizations in signing on to an informational letter of support addressed to Senator Sherrod Brown (D-OH). The letter strongly advocated the submission of the STAAR ACT (Strategies of Address Antimicrobial Resistance) and thanked Senator Brown for his leadership in reintroducing the bill. The STAAR Act, which is designed to help advance antimicrobial stewardship activities and enhance research was reintroduced by Sen Brown on Feb 28, 2018. Sen Brown has for many years been working with researchers and doctors to create the STAAR Act (S2649).

The STAAR Act has a long history, having been introduced to Congress by James Matheson (D-Utah) in 2007 and reintroduced in 2009 and again in 2013 by Matheson. The banner was then carried by Sen Brown with a reintroduction in 2014. APUA has been a consistent supporter since the bill's inception.

The current version would specifically:

- Promote prevention and track antibiotic use and resistance;
- Place greater emphasis on federal antimicrobial resistance surveillance, prevention and control and research efforts;
- Authorize the use of grants to study the development and implementation of antimicrobial stewardship programs
- Allow the CDC to implement prevention collaborative efforts and expand public health partnerships;
- Require annual reports on implementation.

The STAAR ACT, enjoys broad, bi-partisan support, but budget cuts to the Centers for Disease Control could potentially undermine its implementation.

APUA co-signs letter to McDonald's

In February, 2018, APUA joined over 80 other stakeholders--including U.S. PIRG, the National Resources Defense Council, Consumer's Union, Friends of the Earth Food Animal Concerns Trust and Center for Food Safety-- in signing a letter asking McDonald's to commit to a time-bound policy to eliminate serving any meat raised with the routine use of antibiotics. The letter notes that McDonald's became an industry leader in 2016, when it responded to consumer demand to eliminate use of all medically important antibiotics in its U.S. chicken supply as stated in its updated Global Vision for Antibiotic Stewardship in Food Animals. The letter urges McDonald's to expand its stated responsibility by applying a similar policy to the company's beef and pork supplies – specifically, to "require its producers to reserve antibiotics only to treat sick animals or control an identified disease outbreak." The letter suggests that McDonald's influence "can send a clear signal to meat producers and consumers that preserving the efficacy of these precious medicines is a top priority," and should set the bar for other competitors in the fast food industry.

Publications of Interest

Antibiotic Stewardship: Why we must, how we can, by Arjun Srinivasan (U.S. CDC) in Cleveland Clinic J Med (2017) 84:673-679.

Antimicrobial stewardship: A competency-based approach is a new, free, online course available via the OpenWHO platform.; provides participants with an understanding of the core competencies of antimicrobial stewardship and how they may be applied.

Challenges in Antibiotic Resistance: Point Prevalence Surveys—an Online Course; led by experts of the British Society for Antimicrobial Chemotherapy, the course looks at the importance of measuring antibiotic consumption and how to conduct, analyze and learn from a PPS.

The complex relationship between antibiotic use and resistance: why scientists need sophisticated analytical tools to better evaluate changes in agricultural use policies; A PEW Charitable Trusts Analysis by K Holzer (Dec 2017)

Consensus on wound antisepsis : Update 2018 by A Kramer et al in Skin Pharmacol Physiol (2017) 31:28-58; Outlines optimal treatments for chronic wounds, wound decolonization and cavity cleansing, including most promising prospects.

Pathogen distribution and antimicrobial resistance among pediatric healthcare-associated infections reported to the National Healthcare Safety Network, 2011-2014 by JG Lake et al in Infect Control Hosp Epidemiol. (2018) 39:1 -11. The first pediatric-specific description of antimicrobial resistance data reported to the NHSN (US); designed to help identify priority targets in infection control and antimicrobial stewardship.

Fear and hierarchy as drivers for antimicrobial prescribing, a blog by J Otter, commenting on the J Hosp Infect review: Fear and hierarchy: critical influences on antibiotic-decision making in the operating theater by J & A Broom (Dec 2017)

APUA in ACTION, continued…

APUA supports SFAR initiatives

As a member of the Stakeholder Forum on Antimicrobial resistance (S-FAR), APUA has lent its signature of support to letters directed to three new U.S. health care executives: Health and Human Services Secretary Alex Azar; Centers for Disease Control Director, Robert Redfield; and Assistant Secretary for Health Bret Giroir. The letters offer congratulations to the new appointees and continue by describing the current devastating impact of antimicrobial resistant infections. The letters then urge strong support for the initiatives laid out by the CDC and for strengthening collaborations with the Centers for Medicare and Medicaid Services to implement antimicrobial stewardship programs, to support hospital surveillance systems that remain quite weak, and to drive innovation in antibiotic development. Finally, the letters urge support of a One Health approach to the antibiotic resistance problem by addressing AMR in agri-cultural settings.

APUA CHAPTER NEWS

APUA-Cuba

Dianelys Quiñones Pérez extends an invitation to the following international conference:

Antimicrobial resistance from bench to practice

Havana, Cuba • September 26-27, 2018

Venue: Melia Havana

The conference is jointly organized by The Cuban Society of Microbiology and Parasitology with the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the Spanish Society for Infectious Diseases and Clinical Microbiology (SEIMC), The Lancet Infectious Diseases, Clinical Microbiology and Infection, and the Pan American Association of Infectious Diseases (API).

Antibiotic Resistance in the News

Policy Updates

U.S. Veterans Health Administration takes steps to address multidrug resistance "crisis"

As the largest integrated healthcare system in the U.S., the Veterans Health Administration has utilized its unique leadership position to combat the spread of dangerous multidrug resistant organisms (MDROs). In the Feb. 2018 edition of Infection Control and Hospital Epidemiology (Vol 39, Issue 2, pp186-218) the organization has authored a series of five commentaries that will help identify knowledge gaps and set research agenda. The work evolved from a September 2016 research conference of experts which defined topics for four articles:

Transmission dynamics - a focus on the vehicles for disrupting microbial transmission, including hand hygiene, active surveillance, isolation measures and enhanced environmental cleaning.

Antimicrobial stewardship - a focus on optimizing the structures and activities of antimicrobial stewardship teams.

Microbiome - an examination of the framework for microbiome manipulation to eradicate or prevent colonization by resistant pathogens, including further study of fecal microbiota transplantation (FMT) and non-GI targets.

Special populations - an outline of specific care settings in which standard infection control protocols are inadequate or inappropriate, in particular, long-term care, spinal cord injury, rehabilitation, mental health, ambulatory care and home-based care.

SHEA updates guidance on easing contact precautions

Contact precautions are employed in breaking the chain of patient-to-patient transmission. Mechanisms typically involve single occupancy rooms for a patient with suspected superbug infection, and the donning of gloves and gowns for healthcare workers contacting them. Much uncertainty surrounds the removal of this process, primarily because the length of patient colonization is often unclear, since some patients are either persistent carriers or long-term shedders. Consequently, The Society for Healthcare Epidemiology of America (SHEA) has issued four-point recommendations from its panel of experts concerning elimination of contact precautions for antibiotic-resistant infections in acute care hospitals. The guidelines, published in Infection Control and Hospital Epidemiology, were gleaned from evaluation of available literature and a survey of SHEA Research Network institutions, author opinions, practical considerations and potential harm. The findings discuss organism–specific recommendations for discontinuation of contact precautions

APUA lauds track record of long-time antibiotics champion, Louise Slaughter (1929-2018)

Healthcare giant, microbiologist and U.S. Congresswoman (D-NY), Louise Slaughter, passed March 16 at age 88. Aside from her seminal work in nondiscriminatory genetics, Rep. Slaughter was a strong voice against antibiotic overuse, having written her graduate degree thesis on the problem of antibiotic resistance.

Dr. Slaughter was an ardent advocate for reducing the regular of use of medically important antibiotics in healthy food animals and was the first to confirm the statistic that 80% of US antibiotics were used in animal agriculture. She was the original author of PAMTA – Preservation of Antibiotics for Medical Treatment Act – a bill she first introduced to Congress in 1999, and reintroduced annually, after assuming primary sponsorship in 2007. It sought to end the use of 8 medically important classes of antibiotics for growth promotion in healthy animals and to prevent newly introduced antibiotics from harming humans. In 2013, she asked 60 companies in the animal food producing chain to disclose their antibiotic use policies and applied pressure to convince major sellers to adopt antibiotic-free policies. Her staunch support will be sorely missed.

in patients with MRSA, VRE (vancomycin–resistant *Enterococcus*), *Clostridium difficile*, MDR *Enterobacteriaceae* (including carbapenem-resistant forms [CRE] and ESBL-producers). The guidelines are based on cautious, reasonable suggestions in light of insufficient evidence to make formal recommendations for molecular testing. The authors stress the need for further studies in "real-world" settings to address these deficits.

Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) convenes

Government agency representatives from Canada, The European Union, Norway and the U.S. gathered with leading antimicrobial resistance experts in a two-day meeting in Atlanta, Georgia in March to discuss common challenges in addressing antimicrobial resistance. This was the second international in–person gathering of TATFAR, which was originally formed in 2009 and administrated by the CDC to work cooperatively in addressing the threat of antimicrobial resistance (AMR). The group convened for the purpose of capitalizing on partnerships and discussing ongoing work, specifically:

- Maximizing partner engagement to motivate action on AMR;
- Strategies to support local level action and government collaboration on National Action Plans;
- Improving stewardship in the human use of antibiotics;
- Methodologies for measuring animal consumption of antimicrobials

Antimicrobial stewardship

Prophylactic antibiotic use for STIs raises questions

A recent Lancet study out of Paris has demonstrated a dramatic reduction in the rates of certain sexually transmitted infections (STIs) in a group of men who took doxycycline within 24-72 hours following unprotected sex. The intervention resulted in a 70-73% drop in cases of chlamydia and syphilis, but was ineffective for gonorrhea, which is not susceptible to the drug. Syphilis has risen dramatically in recent years, and a short-term intervention (~2 months) could quickly reduce the incidence in certain target groups.

While chlamydia and syphilis have not yet exhibited doxycycline resistance after many decades of use, the proposed practice does raise multiple concerns. Valid criticisms have been raised over "friendly fire injury", i.e., the potential for antibiotic resistance development and/or alterations within the gut microbiome. Moreover, the long-term outcomes are unknown, and potential patient demands for doxycycline are worrisome. Currently, the study authors are only suggesting short–term use in high risk populations, when also combined with other strategies (e.g., frequent STI testing). They conclude that prophylactic use of STIs is premature at this point, and more long-term studies are needed to assess the larger impacts, including reduced condom usage.

Studies document antibiotic excess in hospitalized children / sinus infections

A new large, international survey out of Germany, consisting of 17,693 children from 226 pediatric hospitals in 41 countries found "far too much unnecessary—as well as too much inappropriate—antibiotic prescribing." The 2012, one-day point prevalence study found that nearly 33% of children received one or more antibiotics: ~27% for pre-surgery prophylaxis and ~73% for preventing infection associated with medical conditions. Over 50% of prescriptions were for broad-spectrum antibiotics (e.g., tetracyclines, macrolides, lincosamides) and ~37% involved combinations of two or more antibiotics. New guidelines from the WHO recommend prophylactic antibiotics against surgical site infections just two hours prior to incision for most surgeries, yet in this study, over 80% of surgical prophylaxis occurred more than a day before. The authors found their results not only surprising, but "troubling" and not "evidence-based", suggesting that the high usage rates likely stem from lack of guidelines for medical prophylaxis and the tendency to "play it safe." Noting that children are not simply "small adults", they emphasize an urgent need for improvement, particularly

for pediatric-specific stewardship programs.

In the U.S., antibiotics are prescribed for sinus infections more than for any other illness. Now, a new JAMA Internal Medicine article has reported that these prescriptions are for longer duration than recommended by the IDSA (Infectious Diseases Society of America). The data derive from analysis of 3.7 million adult sinusitis cases in 2016. While current guidelines specify 5-7 days of treatment for uncomplicated infections, the study found that 7-10% received therapy for 10 or more days. Due to current high rates of resistance, azithromycin is no longer recommended. Nonetheless, over 20% of infections were treated with this drug for 5 days. The new guidelines replaced the older adage, which states that shorter durations would not completely eradicate the infections and would risk leading to persistent, recurrent antibiotic-resistant infections. The new guidelines are based on the premise that "if the patient is responding to treatment, five to seven days is safe and is usually enough...longer treatment is not usually needed." The authors speculate that possibly not all doctors have absorbed and adopted the new shorter duration guidelines, which supersede the pre-2012 recommendations for 10-14 days duration.

Epidemiology and Surveillance

Global antibiotic consumption up 65%

An international investigation of global antibiotic use, led by the Center for Disease Dynamics, Economics and Policy, reports antibiotic consumption at 42 billion doses a year in 2015—up 65% over that found in 2000. Per person use has increased by 39%. The data, published in the Proceedings of the National Academy of Sciences, were collected using pharmacy sales data from 76 countries.

While top consumption in 2000 occurred in high-income countries, i.e. France, New Zealand, Spain, Hong Kong and the U.S., the pattern in 2015 shifted more toward the lower and middle income countries of Turkey, Tunisia and Algeria, and now also includes Spain and Greece in the top five. Consumption in the U.S. remains relatively stable at ~3.3 billion doses, with a rate of 28.2 doses per 1000 residents per day, which is down 14% since 2000.

In part, the findings reflect more access by lower income countries, which is considered beneficial, but is still worrisome because use is "catching up" with other nations—often as a means to compensate for the impacts of poor sanitation and water quality. Also of considerable concern is the alarming increase in use in nearly all countries of new and last-resort antibiotics, e.g., the linezolids, carbapenems, and colistin.

At the current growth rate, it is estimated that by 2030, total global antibiotic consumption will grow 202%.

Antibiotic resistance now costs $2B per year in U.S.

Researchers at Emory and St. Louis Universities have reported the first U.S. estimate of incremental costs of antibiotic resistance over a 13 year period—from 2002 to 2014. While the number of bacterial infections has remained fairly constant at 13.5 to 14.3 million, the number of antibiotic-resistant infections has now climbed to 1.6 million (11%)—more than double the number in 2002 (5.2%). Each resistant infection costs on average $1,838 more than a non-resistant one, largely due to the increased costs of inpatient care associated with the failure of initial therapy. The researchers note that their estimate does not include nursing home patients or those in skilled nursing facilities, prisons or other institutional sites, nor does it consider indirect societal cost or expense for infection control or stewardship. They note that the data "make a compelling case for urgent action by national and international policy makers."

Candida auris joins list of worrisome superbugs

For some time, common species of the yeast *Candida* (i.e., *albicans, dubliniensis, parapsilosis. tropicalis, glabrata and kruseri*) have presented a formidable foe in the healthcare setting—invading catheters, ventilator tubes and IV lines—resulting in major morbidity, with up to 47% attributable mortality in severe invasive forms. As of April 2018, 11 different U.S. states have reported a total of 279 cases of a

newly emerging species, *Candida auris*, which has produced some unique challenges with regard to treatment. *C. auris* has demonstrated resistance to the first-line antifungal agent, (e.g., the trizoles), and can possess elevated MICs (minimal inhibitory concentrations) to the three major antifungal classes. In the U.S. cases, ~90% were resistant to fluconazole and 30% resistant to amphotericin B. Further challenges involve misidentification by standard laboratory tests. Only MALDI-TOF (matrix assisted laser desorption ionization time-of-flight) and molecular sequencing methods can adequately differentiate *C. auris* from other *Candida* species. The CDC has recently updated its recommendations for identification of *Candida auris*, including antifungal susceptibility testing.

Consequently, the echinochonidins, with current resistance at ~5%, have become the antifungal drug of choice. These are semisynthetic lipopeptides that attach to the fungal cell wall. While highly effective, fungal resistance can develop quickly, complicating recovery. In cases of drug failure or persistent infection, amphotericin B becomes a backup option—although it is less well tolerated and has potential for severe kidney damage.

On a more positive note, scientists at Case Western Reserve University School of Medicine have discovered a new class of antifungals that show promise against *C. auris* infection, both in vitro, against 16 different global strains—and in a new mouse model of infection. The drug works via a novel mechanism by blocking how essential proteins attach to the cell wall—as opposed to poking holes in the membrane or inhibiting sterol synthesis like other antifungal agents. In *in vitro* studies, the agent is 8-30 times more potent than 9 other available antifungals. Treatment of infected mice demonstrated significant reductions in fungal burden within 2 days—laying the foundation for phase 1 clinical trials in humans.

GLASS: evolving towards global antimicrobial surveillance

In 2015, WHO launched the first Global Antimicrobial Resistance (AMR) Surveillance System. Known as GLASS, it enlists 52 countries globally to contribute susceptibility data on resistant pathogens to foster standardized global reporting of official national AMR data. In Jan 2018, the first GLASS report was released—with surveillance data provided by 40 countries and AMR data from 22 countries. According to Marc Sprenger, director of the WHO's Antimicrobial Resistance Secretariat, "the report confirms the serious situation of antibiotic resistance worldwide." Analysis of over 500,000 isolates of *E. coli, Klebsiella pneumoniae, S. aureus, Streptococcus pneumoniae, Salmonella spp, Shigella* and *N. gonorrhoeae* showed alarmingly high resistance in some countries. The findings (compiled between April–July 2017) were marked by wide ranges in susceptibility as well as in quality and completeness due to large differences in developmental status and surveillance capacities, but are viewed as an "important first step." Of particular note was the finding of *Neisseria gonorrhoeae* with nearly 100% resistance to ceftriaxone and ~15% resistance to azithromycin – the two only remaining treatments. Likewise, nearly 75% of blood isolates of *Acinetobacter* from S. Korea were resistant to carbapenems. The WHO interactive database represents an important advancement towards obtaining coordinated, standardized, country-based data that intend to perceive the antimicrobial resistance problem at a global level.

CDC updates Antibiotic Resistance Investment Map

Since 2016, the U.S. Centers for Disease Control has invested $144 million to state and local health departments as part of its Antibiotic Resistance Solutions Initiative (ARSI) to curb the spread of drug-resistant bacteria. These investments are tracked via an interactive online tool: the Antibiotic Investment Map, which showcases 170 success stories from fiscal year 2017 that can be printed as state and city-specific fact sheets. Among its notable accomplishments are:

- Reduction of CRE (carbapenem-resistant *Entero-bacteriaeae* by 30% in 40 Michigan healthcare facilities;
- Identification and containment of an outbreak of imipenem -resistant *Enterobacteriaceae* in Iowa;
- Installation of antibiotic resistance epidemiologists across

Texas

- Institution of whole-genome sequencing for outbreak surveillance of common food and animals pathogens (*Listeria, Salmonella, Campylobacter, E. coli*) in 38 states.
- Specialized diagnostics for identifying emerging drug-resistant *Candida auris* (see news article on p.13) in New York
- Expanded testing for multidrug-resistant gonorrhea in New York to halt transmission in high risk communities.

Of chief concern at present are proposed cuts (14% to ARSI) to the 2018 budget that could undermine the future of U.S. surveillance efforts and its leadership in global efforts to control antibiotic resistance.

Association found between childhood antibiotic exposure and lifetime diseases

In a recent talk, titled, "The Dark Side of Antibiotics", Martin Blaser, director of the Human Microbiome Program at NYU School of Medicine, revealed some very interesting associations between early childhood exposure to antibiotics (0-3 years) and possible "powerful metabolic effects" on the gut microbiome.

Noting that U.S. infants receive an average of three antibiotic courses by the age of two; Pakistani infants receive ~10 courses; and Chinese children carry traces of 18 different antibiotics in their blood and urine, Blaser has observed some profound correlations with lifetime diseases. For example:

- In Finland: the more antibiotics that children received, the higher the risk of having a milk allergy;
- In Denmark: higher childhood antibiotic use resulted in a greater risk for Type 2 diabetes;
- In the UK, greater exposure to antibiotics in the first 6 months was linked with increased weight gain.

Because these microbiome changes are passed on to offspring, and produce long-term effects, Blaser is concerned that our current antibiotic use will slowly erode the diversity of the human microbiome. To reverse this trend, Blaser advocates reducing antibiotic use, both in food –producing animals and in human medicine. He envisions a future in which infant microbiomes will be screened, and any missing, essential microbes will then be supplied via replacement therapy.

Colistin: a valuable last-line antibiotic is compromised

For the first time in the U.S., antibiotic resistance has now appeared to the valuable last-line antibiotic, colistin. The resistance emerged in *Klebsiella pneumoniae* isolates derived from the urine of two Atlanta, Georgia patients and were already resistant to carbapenems. Emory University microbiologists sounded the alarm about a "worrisome and underappreciated phenomenon" that goes undetected by the standard tests—a heterogeneity of phenotypes, ie., the presence of a small subpopulation of resistant bacteria that are otherwise genetically identical to all other cells in the culture, but which could thwart the efficacy of colistin treatment. The resistant subpopulation could be observed by allowing growth for an additional 24 hours. Because the genes responsible for colistin resistance were seen to turn on and off, the scientists speculate that maintaining colistin resistance consistently is disadvantageous to the host cell and therefore, not sustainable.

Various strains of *Klebsiella* are responsible for an estimated 10% of healthcare-acquired infections.

Antibiotic failure in post-op infections **found "extremely worrying" and potentially "catastrophic"**

According to a recent Lancet study, one in eight patients undergoing gastrointestinal surgery develops an infection. Of these, one-fifth are found to be antibiotic resistant. The Edinburgh-based study tracked over 13,000 patients from 66 countries globally and found the highest resistance levels in the poorest countries, where infection rates were almost 25%, and more than one-third of these were resistant. In high-income countries, nearly one in ten patients experiences infection, with 17% having antibiotic resistance. The research team blames the high resistance levels on overprescribing—particularly in developing countries. The study is the first of its kind to provide

detailed evidence for examining links between prescribing habits and antibiotic resistance globally.

U.S. sales of animal antibiotics show decline for first time

Between the years 2009 and 2015, the domestic sale of antibiotics approved for use in food animals increased a worrisome total of 24%. In February 2018, the FDA released a report announcing a first-time decline of 10% observed between 2015-2016—a decrease of 14% in those antibiotics that are medically important for humans. Medically important drugs still account for 60% of food animal use. The most commonly used class, the tetracyclines, dropped by 15%, while lincosamide and cephalosporin sales fell by 22% and 4%, respectively. The statistics reveal that medically important antibiotics are used at higher rates in beef (43%), pork (37%) and turkey (9%), than in chickens (6%).

These stats only reflect the amounts purchased, and not the volumes actually used by farmers. The FDA is considering a more accurate method already adopted in Europe that would adjust sales data by taking into account the actual weight and size of the herd population.

The downward trend may be a reflection of consumer demands for antibiotic-free meat, but does not yet reflect the impacts of the FDA Guidance for Industry (GFI) #213, which went into effect on Jan 1, 2017. That ruling prohibits medically useful antibiotics for growth promotion and also requires veterinary oversight of antibiotic use for disease prevention and treatment.

Chilean Salmon farms top agricultural antibiotic consumption

According to a recent report by Oceana, salmon farms in southern Chile (second only to Norway in production volume) use up to 950 grams of antibiotics to produce one ton of fish. In contrast, Norway uses 0.17g per ton of salmon, while the notoriously high-use pork industry uses 172 grams per ton. The Oceana report is the first to delineate antibiotic use on a company by company basis. Experts are not so much concerned about the human consumption of drug residues, since fish are weaned off antibiotics prior to harvest and processing. The real worry is the potential for uptake and transfer of antibiotic resistance genes that are amplified in the ideal breeding grounds fostered in the salmon pens: densely packed fish, feces, feed residue, delousing chemicals and antibiotics. In Chilean farms, the massive antibiotic doses stem from the ravages of a unique disease—piscirickettsiosis—a hemorrhagic bacterial disease against which the veterinary antibiotic florfenicol is the primary drug of choice. The concern for humans is that florfenicol resistance is linked and transmitted with genes coding for resistance to human-use antibiotics.

U.S. trade regulations are too vague to identify the sources for U.S. consumers, but some major grocery chains have either reduced or deleted their Chilean sources. According to Oceana spokesperson Leisbeth van der Meer, ultimately it is the informed consumer that will demand a cleaner, transparent industry.

Developments in antimicrobial drug therapy

Dirt yields new antimicrobial family: the malacidins

Using gene sequencing techniques to analyze over 1,000 diverse soil samples collected by citizen scientists from across the U.S., scientists at New York's Rockefeller University have discovered a world of unknown compounds, and among them, a novel family of antibiotic compounds—the malicidins. The compounds were uncovered initially through a search for a specific gene associated with the production of calcium-dependent antibiotics—an "on-off switch" that is believed to thwart development of antibiotic resistance. Once identified and cloned into an organism that could be cultured, the organism began producing malacidins, which could attack bacterial cell walls. These compounds were found to kill several superbugs and to eliminate skin wound infections in rats infected with MRSA—all without developing resistance. The research team acknowledges the long road ahead to produce an effective drug for clinical use

APUA

"Preserving the Power of Antibiotics" ®

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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