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Turning the Tide: Incentivizing Antibiotic Development and Stewardship

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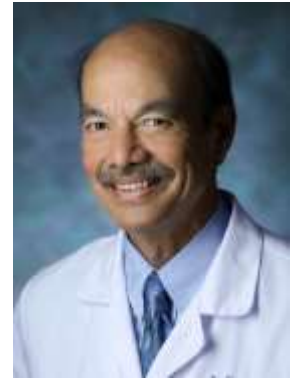
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Heath

“UTI”:An Old Diagnosis in a New World

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Finucane

As currently construed, urinary tract infection, or “UTI”, is diagnosed in a variety of clinical situations ranging from the trivial to the fatal (Table 1). Harmful overtreatment is commonplace. “Significant bacteriuria,” on which most diagnoses are based, refers to findings on agar-based cultures (we will call this standard bacteriuria), first used in the 1880s. It is defined as the occurrence of $>10^5$ /ml bacteria on a blood agar plate. “Significant bacteriuria” has no significance in identifying patients who will benefit from antibiotic treatment. Genetic techniques, expanded culture and other modern diagnostic methods show that the healthy urinary tract hosts a complex, generally beneficial microbiome and a virome. Current management strategies, deeply flawed on their own terms, now also require a conviction that only bacteria detected by standard cultures can be pathogenic and that organisms that do not grow on standard cultures may be safely ignored.

Representative problems in common practice

Two presentations of “UTI” are particularly troubling. The first is acute dysuria, considered synonymous with “UTI” by many patients and some clinicians. One strategy is simply to treat such patients. Perhaps more commonly, laboratory evaluation is ordered and if the patient has standard bacteriuria, antibiotic treatment is given. About half of symptomatic patients will have “significant bacteriuria.”¹ This standard-of-

care approach to treating acute uncomplicated cystitis ignores two important facts. First, both standard bacteriuria and urinary symptoms frequently resolve and recur spontaneously.²⁻⁴ Second, subsequent pyelonephritis is rare and the incidence does not seem to be reduced by antibiotic treatment.⁵ “Acute uncomplicated cystitis rarely progresses to severe disease, even if untreated; thus, the primary goal of treatment is to ameliorate symptoms”⁶. For eons, and at present in under-resourced settings, acute uncomplicated cystitis has not been treated with antibiotics, and severe illness or lasting ill-effects are very rare.

Pain resolves more quickly with antibiotics; however, a safe effective analgesic would reduce much antibiotic overuse with little or no risk.

“Significant bacteriuria” has no significance in identifying patients who will benefit from antibiotic treatment.

The second lamentable use of the diagnosis of “UTI” is seen when frail older patients with altered mental status or altered color or odor of urine are found to have bacteriuria.⁷ In patients who are otherwise well, no evidence shows that delirium outcomes are improved by antibiotic treatment and patients may certainly be harmed. Guidelines and consensus statements recommend against such practice (Table 2).⁸ Treatment to improve the odor or appearance of urine is mentioned only to condemn the practice. Ceftriaxone should rarely be used to deodorize urine. Because the term “UTI” can be applied, however, treatment commonly follows.⁹ In older women living in institutions, the prevalence of standard

asymptomatic bacteriuria (ASB) can approach 50%, so the likelihood of finding incidental bacteriuria is high.¹⁰ In a prospective cohort study of 343 delirious patients with ASB, those treated with antibiotics had no difference in functional recovery but had a higher rate of *C. difficile* disease.¹¹

The era of the microbiome Overtreatment of “UTI” based on a finding of standard bacteriuria is widespread. With new evidence

about the urinary microbiome, antibiotic treatment is ever more indefensible. Gene-sequencing and sophisticated culture techniques show that “asymptomatic bacteriuria” is not a diagnosis but the normal state of a healthy urinary tract.¹² The discovery of this urinary microbiome suggests clinicians have been focusing on a small part of a much larger picture and assuming that bacteriuria is an unusual and harmful event.¹³

Demonstration of the microbiome has 2 direct implications. First, attributing dysuria, delirium, falls, reduced functionality, odoriferous or discolored urine, etc. to standard bacteriuria can only be justified if all bacteria that are possibly pathogenic can be identified using agar-based cultures, and that any bacteria that cannot be seen easily should be ignored. Second, stable microbiomes seem to provide benefit to patients and antibiotic disruption may cause important harm. In the gut, *C. difficile* disease is a notorious example.

Cai et al studied a group of women who had recurrent “symptomatic UTI” and were later found on screening to have ASB. Half were randomized to receive antibiotic treatment and this group had higher rates of symptomatic recurrence over the next year than those randomized to receive no treatment. The authors concluded that asymptomatic bacteriuria “may play a protective role in preventing symptomatic recurrence.”¹⁴ Unmentioned was the stable but uncultivable microbial com-

Table 1. Clinical situations sometimes diagnosed as “UTI”

◆ **Presence of “significant bacteriuria”***

- by itself
- with dysuria
- with change in mental or functional status
- with change in odor or color of urine
- with bacteremia and same organism in blood and urine
- with “flank pain” and signs of invasive infection
- with nonspecific symptoms such as dizziness, fatigue, falls, seizure

◆ Presence of dysuria (or sometimes other urinary tract symptoms) regardless of bacteriuria

*“Bacteriuria” refers to findings on conventional cultures, defined as >10⁵ cfu/ml.

munity that surely contributed.

Conclusion

Antibiotic treatment of “UTI” generally provides little or no benefit to patients who are not systemically ill. Treatment shortens duration of dysuria in patients with acute uncomplicated cystitis and benefits patients with asymptomatic bacteriuria who are pregnant or soon to undergo urologic procedures. Patients with incident confusion who are found to have bacteriuria have not been shown to benefit from treatment, and expert advice opposes defining, diagnosing or treating this syndrome as a “UTI.” The harm, without benefit, of treating ASB, with the exceptions noted above, has long been known, but the practice continues unabated. Recognition that the natural state of the healthy urinary tract is ASB should have some impact on this dismal practice.

The willingness to blame acute symptoms on bacteriuria should be tempered by the knowledge that everyone is bacteriuric all the time and that stable microbial communities are generally beneficial. Antibiotic treatment based on agar-based culture results is an obsolete and harmful practice. As Costello and colleagues note, “transitioning clinical practice from the Body-as-Battleground to the Human-as-Habitat perspective will require rethinking how one manages the human body”.¹⁵ Patient safety and public health can be improved immediately

Table 2. Expert advice on definition, need for testing and need for treatment of "UTI" in patients with incident delirium who are in long-term care and are not catheterized⁸

Advice	Source
<i>A patient with delirium and bacteriuria does not meet the definition of "UTI."</i>	Surveillance Definitions of Infections in Long-Term Care Facilities: Revisiting the McGeer Criteria. ¹⁶
<i>Evaluation for "UTI" is not recommended for patients with delirium, bacteriuria and fever.</i>	Clinical Practice Guideline for the Evaluation of Fever and Infection in Older Adult Residents of Long-Term Care Facilities: 2008 Update by the IDSA ¹⁷
<i>Antibiotic treatment for UTI is not recommended for a patient with delirium, bacteriuria, and fever. (Elsewhere in the Consensus, however, antibiotic treatment for the combination of fever and delirium is accepted, without reference to urinary tract findings.)</i>	Development of Minimum Criteria for the Initiation of Antibiotics in Residents of Long-Term Care Facilities: Results of a Consensus Conference ¹⁸
<i>Don't use antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present.</i>	American Geriatrics Society identifies five things that healthcare providers and patients should question ¹⁹

by acting on what is known about standard bacteriuria. As the science of the microbiome matures, the term "UTI" will join "ague" and "dropsy" in the category of illnesses that time has passed by.

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World Antibiotic Awareness Week : November 13-19



Upcoming Events

November 13, 2017

Educational webinar: The role of point of care C-reactive protein testing in reducing inappropriate antibiotic use; presented by Liz Cross, University of Hertfordshire, UK; produced by Whitehat Communications and sponsored by Alere

November 13-19, 2017

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

October 29-November 1, 2017

Antimicrobial and Resistance: Opportunities and Challenges (T4), A Keystone Symposia Conference, organizers: Gautam Dantas and Jennifer Leeds, Santa Fe, New Mexico, USA

Jan 19-20, 2018

ICAR 2018: International Congress on Antimicrobial Resistance, Thanajvur, India

February 22-24, 2018

Annual Scientific Meeting Antimicrobials 2018, Brisbane Australia

April 14-15, 2018

15th Annual Global Health & Innovation Conference Yale University, New Haven, Connecticut

April 21-24, 2018

ECCMID 2018: 28th European Congress of Clinical Microbiology and Infectious Diseases, Madrid, Spain,

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

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



Antibiotics – The Last Frontier

David Shlaes, MD, Anti-infectives Consulting LLC (retired)

Dr. Shlaes owns the blog: [Antibiotics - The Perfect Storm](#)

In 2010 my book, “Antibiotics – The Perfect Storm” was published.¹ (I use the term antibiotics to include any small molecule antibacterial drug). At that time there was (and still is today) an increasing frequency of bacterial resistance to even our antibiotics of “last resort.” The perfect storm consisted of a number of converging pressures on our ability to maintain any kind of reasonable pipeline of new antibiotics in the face of this public health threat as shown in Box 1.

As a result of this “perfect storm”, our antibiotic pipeline is dangerously thin as demonstrated by a recent report from the World Health Organization.²

Some things are looking brighter today. We are making slow but important progress in our scientific understanding of antibacterial drug discovery especially for those difficult to target gram-negative pathogens.³

BOX 1

Antibiotics – The Perfect Storm (2010)¹

- Bacteria are becoming resistant to antibiotics faster than we can find new ones.
- Discovering new drugs is hard.
- The FDA is living on another planet.
- The market for antibiotics is soft.
- Industry is consolidating faster than a speeding bullet.
- Companies continue to abandon antibiotics research.

The FDA⁴ and the European Medicines Agency⁵ have provided a number of streamlined clinical development pathways for antibiotics active against key resistant pathogens that will save time and money and will get those new products to patients

and their physicians in a timelier manner. Encouraged by these developments, some pharmaceutical companies have restarted their antibiotic research efforts, although the total number of large companies engaged in the area has not really changed since 2010.⁶

The Biomedical Advanced Research and Development Authority of the Department of Health and Human Services in the U.S. and the Innovative Medicines Initiative in Europe have been providing substantial financial support to companies trying to develop new antibiotics of high priority.⁷ These “push” incentives reduce costs for any given product considerably – but this will not be enough.

We are beginning to make progress on training a new generation of antibiotic hunters. A collaboration between CARB-X* and GARDP** has begun to put together a series of workshops, lectures and webinars aimed at training researchers in key aspects of antibiotic discovery and development. The first series of workshops occurred at the 2017 ASM-ESCMID meeting in Boston and were called Antibiotic Bootcamps.⁸ (They covered early discovery, manufacturing and microbiology). More are planned for the near future.

One area where we have made no progress is the economics of the antibiotic market. A summary of sales for recently approved antibiotics is shown in Table 1. These sales figures pale in comparison to drugs for cancer, psychiatric disease and cardiovascular disease.

One aspect of the market that people fail to understand is that

*CARB-X = A Boston-based international collaboration, *Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator*

**GARDP = *Global Antibiotic Research and Development Partnership*

Table 1. Sales of Recently Approved Antibiotics¹²

Antibiotic	Year of U.S. Regulatory Approval	2015 Sales (Millions USD)
Ceftazidime-avibactam	2015	35.8
Tedizolid	2014	37
Dalbavancin	2014	20.3
Oritavancin	2014	9.1
Fidamoxicin	2011	39.8
Ceftaroline	2010	118.5
Telavancin	2009	9.4

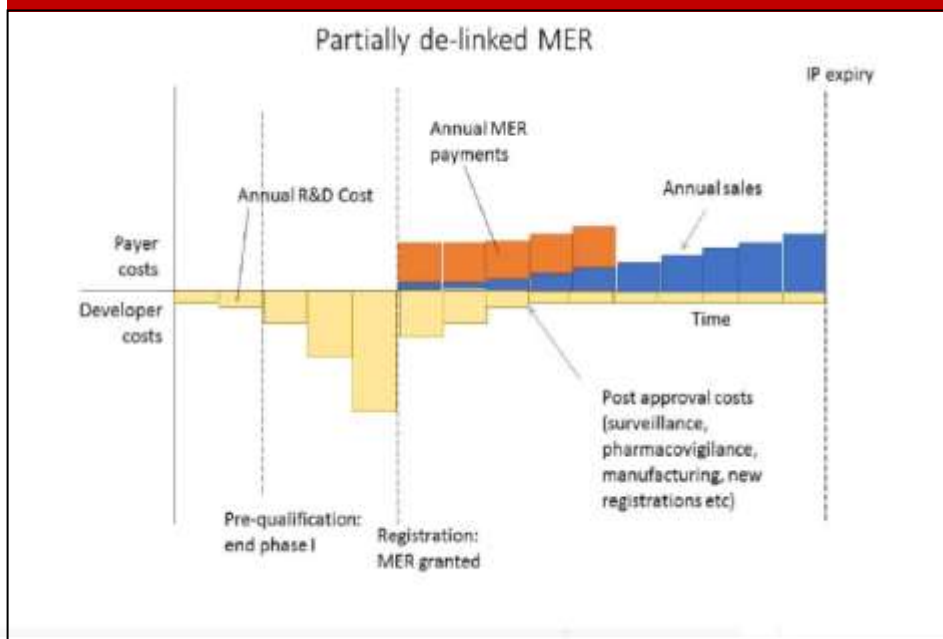
the major cost for a company is not directly related to the product in question. It is the cost of all the prior failures.⁹ And, in the drug discovery and development world, failure is the general rule. Over 95% of compounds discovered in the laboratory will never make it into human trials. Of the small number that do enter clinical development, only 20% or so will actually be approved and enter the marketplace. It is the enormous cost of all these failures that make drug discovery and development such a high-risk endeavor. The most recent estimate of these costs for a single drug was \$2.6 billion.⁹ And it is these costs that any product making it all the way to the market must pay in addition to some profit for shareholders of these companies and to fund further research. Clearly, the antibiotic market is unable to provide these required returns on investment.

Over the last several years, a number of proposals have been presented to address the failed market for antibiotics.¹⁰⁻¹² They all come down to some sort of guaranteed payment at the time of market entry. One

example of this was recently proposed by Drive-AB, a European project to propose solutions to the antimicrobial resistance problem (Figure 1).¹³ As shown in this example, a market entry award would start paying a company at the time they received approval for their new antibiotic that had previously been designated a candidate for such an award based on medical need and priorities such as those proposed by the Centers for Disease Control in the U.S. or the WHO.^{14,15} The continued availability of award payments would be contingent on the company meeting certain predetermined milestones around manufacturing, physician education, and other key elements. In this particular formulation, the company would also be allowed to charge some price for the antibiotic and this price might grow after the market entry reward payments ceased. Drive-AB has suggested, based on mathematical simulations, that such a market entry reward would ultimately quadruple the number of new antibiotics approvals.¹³

Several other market solutions have been proposed and discussed.^{10-13, 15} One, for example, would provide a guaranteed purchase of a given product over time as a kind of insurance or, as some would say, something like fire extinguishers and fire departments.¹⁶ We pay for them but hope never to use them. In another, we provide an exclusivity voucher such that the recipient is awarded an additional period of exclusivity for a product

Figure 1. One model for a Market Entry Reward (MER)¹³



of their choice from their portfolio.¹² This voucher could be kept or sold. Of course, its monetary benefit would have to be capped and the award would still be subject to contractual constraints, as would be true of all the market entry rewards being discussed.¹² All these proposals come down to a societal determination of the value of antibiotics in general and the particular product specifically. All also depend on government intervention to provide any payment regardless of the particular solution under discussion. The differences among all the proposals revolve around how the payments are funded by society. Does it come from general revenues spread out among all taxpayers—or does it come from only specific subpopulations of taxpayers?

There is no doubt that the antibiotic pipeline today is in dire straits.² Regardless of the incentive model one prefers, there is no question that unless we do something soon to address the failure of the antibiotic market, our pipeline of new antibiotics and our ability to deal with bacterial infections in the future will suffer further. We risk losing the miracle of antibiotics for our children and grandchildren. Lets invest today to prevent that unimaginable outcome.

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Antibiotic Resistance Initiatives: **What's Happening in India?**

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It is true that India was late in initiating serious efforts to tackle antimicrobial resistance (AMR).

With more than a billion population, 75,000 hospitals, one million doctors, half a million pharmacies, and inadequate infection control facilities in hospitals, socio economic disparity and sanitation issues in the community, tackling antimicrobial resistance in the current Indian scenario is a huge and complicated task. A heavy burden of tropical infections; inadequate training on rational antibiotic use in undergraduate and post graduate medical curriculum; the absence of clinical pharmacists that support good quality prescribing; and the tendency for clinicians to focus concern only on good clinical outcomes for individual patients (regardless of their commitment to the broader public good) make the issue more intricate.^{1,2,3}

In 2011, the Indian Health Ministry published a National Policy for Containment of Antimicrobial Resistance.⁴

Unfortunately, implementation of the policy was delayed, primarily due to the well-intentioned, but unrealistic recommendation of a complete ban on over-the-counter (OTC, non prescription) sale of all antibiotics, as well as to an inadequate political will to implement the comprehensive policy.

Considering the dire significance of the AMR scenario in the country, medical societies in India came forward in a very

coordinated and focused way, compiled the “Chennai Declaration” recommendations, and mobilized stake holders—including all medical societies and the government—to initiate implementation of the National Policy. The first step was to make the necessary amendments to the National Policy in order to make it suitable to the backdrop of the Indian scenario.^{1,2,3}

The Chennai Declaration provided a practical and implementable solution suitable to the background scenario of heterogeneity of health care system in the country. The Chennai Declaration recommended a “step by step” strategy for regulating OTC sale of antibiotics, starting with second-

and third-line antibiotics.^{2,3,5}

As stated by the Declaration itself: “It is obvious that a ban of over-the-counter (OTC) sale of all antibiotics without prescription will be the ideal step.

“It is obvious that ban of over-the-counter (OTC) sale of all antibiotics without prescription will be the ideal step...but whether such a strict policy could be implemented is questionable.”

Currently, all antibiotics, including injectables, can be purchased OTC without prescription. It is very easy to issue an order to ban OTC sales of all antibiotics, but whether such a strict policy could be implemented is questionable. It is debatable whether we have enough drug inspectors and infrastructure to monitor OTC dispensing of all antibiotics. This should be taken into consideration while making any recommendations. An over-enthusiastic approach without proper planning will only lead to failure of the overall

strategy and may further affect success of the overall antibiotic policy. A practical approach will be to formulate a list of antibiotics with strict monitoring on the dispensing of these drugs. Step-by-step introduction of other drugs to the restricted list could be tried once the success of the first stage is ensured.”³

In 2013, in accordance with the Chennai Declaration recommendations, the Ministry of Health issued a new rule (modified H1 rule) that targets 24 antibiotics and 11 anti-tuberculosis drugs, for which pharmacists not only must insist on a prescription by a registered medical practitioner, but also must record details about the patient, medication and the prescriber. First-line antibiotics are excluded from the H1 list and so will not come under the strict monitoring. Although pharmacists had no objection to the relatively liberal list of antibiotics, the strict norms of documentation and record keeping resulted in suboptimal success of the modified H1 rule.^{2,3,5}

In 2016, the Health Ministry published its *National Treatment Guidelines*, providing a comprehensive but practical approach to antibiotic selection to infectious disease entities prevalent in the country.⁶

Indian hospitals are especially affected by the challenge of gram-negative “superbugs.” Tens of thousands of hospitals in India, lacking the consistent infrastructure necessary for the practice of good infection control, coupled with the sheer size of the country’s gram-negative bacterial challenge, are the major deterrents to compiling uniform infection control recommendations for all hospitals. In 2017, The Indian Health Ministry published its draft *National Infection Control Guidelines* (Fig 1), a document that will guide better infection control practices and serve as a prototype for infection control manuals in all hospitals in India.⁷ A “best of the ability approach” to contain the spread of these bacteria may be the practical and implementable methodology in the Indian scenario. Hospitals with good infrastructure must

follow all precautions to the best possible extent, while hospitals with resource constraints should follow precautions to the best of their ability and affordability.

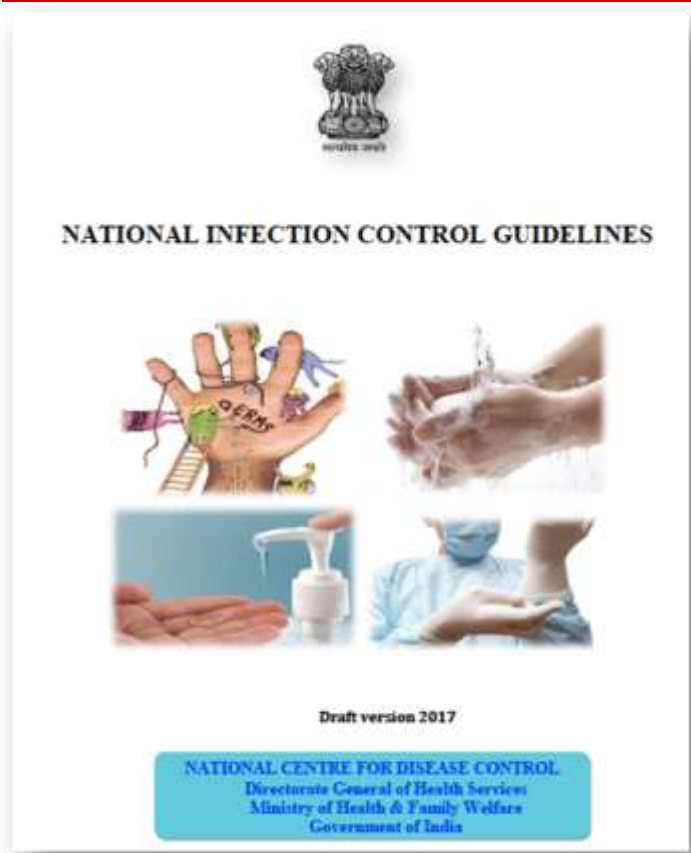
In re-emerging economies like India, improving sanitation in the community and in hospitals should be the supreme objective of an AMR action plan. Unless we answer the sanitation question, all the other components will be futile, superfluous and cosmetic. In essence, The “Swachh Bharat Abhiyan” (Clean India Mission)—a very ambitious plan proposed by the Indian Prime Minister—will be the most important AMR initiative in the country. India’s national action plan must be centered on Swachh Bharat Abhiyan.

In 2017, India prepared a *National AMR Action Plan*,⁸ in tune with the WHO action plan. The Union Health Ministry has

“Sanitation is more important than political independence.”

Mahatma Gandhi

Figure 1. India’s draft guidelines and prototype for better infection control in all Indian hospitals⁷



called for a meeting of the health secretaries of 29 Indian states and 7 Union territories to explore ways of implementing the country's National Action Plan on Antimicrobial Resistance. In India, health care is predominantly under the jurisdiction of individual states. Even though the National Antibiotic Policy and Action Plan are prepared by the Union Health Ministry, implementation of the recommendations at the grass roots level falls on the shoulder of the states. On October 11, 2017, the Chief Minister of the Kerala state made a landmark announcement on initiation of National Action Plan implementation in that state.

Better late than never!

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Antimicrobial resistance in the next 30 years, humankind, bugs and drugs: a visionary approach by M Bassetti et al in Intensive Care Med July 21, 2017. A multinational team describes current standards of care, recent advances with AMR and prospective overview of next 30 years.

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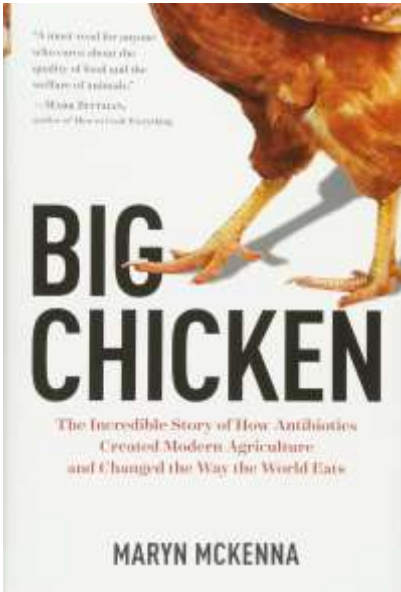
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APUA in Action

APUA Leadership Award Winner
Maryn McKenna releases new book



In her latest provocative narrative, acclaimed health journalist and *National Geographic* contributor Maryn McKenna documents how antibiotics transformed chicken from local delicacy to industrial commodity. **BIG CHICKEN** is the story of how we came to give antibiotics routinely to most of the

meat animals on the planet — and how we discovered that was a terrible idea, the source of an epidemic of drug-resistant infections — wrapped in the story of the rise of industrial poultry production, from the first experiments that demonstrated the effect of “growth promoter” antibiotic doses, to new moves by big companies to forego antibiotic use.

Maryn McKenna’s [TED Talk](#), “What do we do when antibiotics don’t work any more?” has been viewed more than 1.5 million times.

President Levy informs *Technoskeptic* and *Smithsonian* articles on triclosan and fish antibiotics

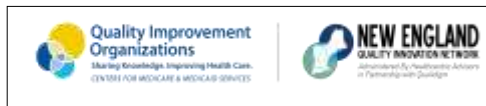
In an August 2017 [Technoskeptic article](#), author Lorenzo Migliorato delves into the history and rationale behind soap additives—in particular that of triclosan, which has now, after many years of pervasive use, been banned by the FDA from personal care products—(along with 18 other chemicals)—with the exception of toothpaste, for which it has

demonstrated efficacy in reducing gum disease. Originally employed solely in the hospital setting, triclosan crept gradually into a multitude of home-based personal hygiene products, paints, plastics, etc. Chemical residues flushed into drains and sewers now persist widely in the environment, posing multiple health concerns.

In his article, Migliorato draws upon the expertise of Drs. Stuart Levy, Timothy Burke and Mark Webber to explain the case for removal of triclosan and other unnecessary chemicals from household soaps and hygiene products. Concerns over triclosan’s perceived capacity to induce cross-resistance to antibiotics have persisted since the time of Levy’s discovery that triclosan acted upon a single gene target. A recent [UK study](#) further amplified these concerns by demonstrating a link between a major mechanism of resistance to antibiotics and resistance to triclosan.

In its July [posting](#), *Smithsonian.com* has spotlighted the troubling internet reports of people taking antibiotics intended for ornamental fish. According to Stuart Levy, this practice goes back several decades, and has been reported among pet store owners, owners of ornamental fish, and the military—all seeking an alternative to costly doctor visits and formal prescriptions. Fish antibiotics are very similar to human ones—often containing amoxicillin, penicillin, erythromycin and ciprofloxacin for example. But, because they constitute such a small fraction of total antibiotic use, they have gone completely unregulated by the FDA, with no real guarantees of drug levels or purity. The prevalence of the misuse is unknown, but is currently under FDA scrutiny. As Levy and others remark, the lack of physician oversight in this self-prescribing trend is worrying, since no diagnostics are performed to confirm bacterial illness or susceptibility to the antibiotics used. Some stores and web sites have since removed these unregulated antibiotic supplies.

APUA joins consulting team for QIN-QIO



APUA is pleased to announce that it has joined a

team of consultants that lends advisory support to the activities of The New England Quality Innovation Network-Quality Improvement Organization. NE QIN-QIO is a collaborative effort between Healthcentric Advisors and Qualidigm that serves as a centralized resource for knowledge to help providers improve care for Medicare beneficiaries, their families and caregivers across New England. QIN-QIO convenes healthcare professional and stakeholders at the local level to connect, share lessons learned, and utilize data to drive improvement. Led by the Centers for Medicare & Medicaid Services (CMS), the Quality Improvement Organization program is one of the largest federal programs dedicated to improving health care quality at the local community level. While the organization has multiple areas of healthcare focus, APUA looks forward to sharing its knowledge in matters related to education on antibiotic resistance, and the advancement of the principles of antimicrobial stewardship.

At a September teleconference, APUA staff scientist, Bonnie Marshall introduced APUA to QIN-QIO team members and summarized current activities and resources.

APUA CHAPTER NEWS

APUA-Nepal

President Kamud K. Kafle has shared that on Sept 17, 2017, the 1st North American Regional Conference of the World Newah Organization was held in Mississauga, Canada. The aim of the conference is to unite the Nepalese community living within the North American continent and abroad in order to promote and preserve Nepalese cultural heritage. A souvenir publication of that meeting featured a short report submitted by Dr. Kafle, titled *National Actions to Combat Antimicrobial Resistance (AMR) in Nepal*. The report informed the community of the increasing and challenging threat posed by antimicrobial

resistance and outlined the following actions taken by the Nepal government to address the problem and protect the Nepalese people from the health risks posed by AMR: 1) steps taken to manage and monitor antibiotic use; 2) enactment of National Antibiotic Treatment Guidelines; and 3) constitution of a national steering committee and alliance for developing a National AMR Containment Policy and Action Plan, 2016.

APUA-Lebanon

President Ziad Daoud has shared the following updates:

- ◆ In the context of its interest in the “One Health Concept”, the APUA-Lebanon chapter implemented (in collaboration with the University of Balamand-Faculty of Medicine and the Lebanese Ministry of Agriculture) a nationwide study on the occurrence of multi-drug-resistant organisms in Lebanese animals. A total of 1650 fecal samples were collected from chicken farms and 260 fecal samples from pig farms countrywide. In addition, workers and environments were sampled. Study results and analysis are currently in preparation for journal submission. Three abstracts will be submitted to the 2018 ASM meeting (Atlanta, GA).
- ◆ In partnership with the World Health Organization and the Lebanese Ministry of Public Health, the APUA-Lebanon chapter has been invited to participate in 6 workshops aimed at training clinical microbiologists in WHONET software. These workshops target 20 Lebanese hospitals and are organized in the framework of the GLASS project. The workshops will be held November 10, 17, 23 and December 1, 6, and 8, 2017.
- ◆ APUA-Lebanon is participating in a study led by the Lebanese Society for Infectious Diseases and Clinical Microbiology and aimed at collecting the antimicrobial susceptibility data of bacterial isolates from Lebanese hospitals in 2017. The APUA-Lebanon chapter is represented by 10 hospitals in this nationwide survey.

Antibiotic Resistance in the News

Policy Updates

EU phases out zinc supplement in swine production

In European swine husbandry, zinc application is a key substitute for sub-therapeutic antibiotic use. Low-dose zinc (150 ppm) is applied to weaners as a nutritional supplement; in the form of high-dose zinc oxide (2,500 ppm), it is effective for prophylaxis and control of post-weaning diarrhea. However, much is excreted, ending up on farmlands via manure fertilizer. Although heavily contested in the U.K., it is argued by some, particularly France, The Netherlands and Denmark that the zinc oxide contamination is associated with certain antimicrobial effects—in particular MRSA.

In view of the potentially serious impacts on the environment, the European Commission voted in June to phase out the use of high level zinc oxide in swine production over the next 5 years. The decision will leave farmers seeking yet another alternative to protect piglets from post-weaning diarrhea.

WHO report confirms dire status of antibiotics

In September, the WHO launched its report, Antibacterial agents in clinical development—an analysis of the antibacterial clinical development pipeline, including tuberculosis, which shows a serious shortage of novel antibiotics to treat the most multiply antibiotic-resistant infections, in particular tuberculosis. The report notes 51 new antibiotics/biologicals are being developed for 12 priority pathogens—with only 8 classified as truly innovative treatments. Treatment options are seriously lacking for MDR and XDR tuberculosis, *Acinetobacter* and *Enterobacteriaceae*. Also, few oral antibiotics are pending for community-based infections and for resource-limited settings.

To address the threat, WHO and the Drugs for Neglected Diseases Initiative (DNDi) have established GARDP — the Global Antibiotic Research and Development Partnership. To date, €56 million have been pledged to GARDP efforts by the Wellcome Trust, several European countries and South Africa.

November 13-19, 2017

Watch for the CDC's launch of **Be Antibiotics Aware**, which coincides with the 10th Annual U.S. Antibiotic Awareness Week (formerly *Get Smart about Antibiotics Week*) and is part of the global *World Antibiotic Awareness Week*.



Antimicrobial stewardship

Challenging the prevailing wisdom: when to stop taking antibiotics

For decades, the prevailing view has been that, once started, a course of antibiotics should be completed in order to prevent the emergence of resistant bacterial strains. However, in a recent issue of the British Medical Journal, Martin Llewelyn and colleagues have challenged this time-honored practice, declaring that the concept is not supported by the evidence.

Alexander Fleming originally advised taking “enough” penicillin to prevent the transmission of an infection to another individual. This piece of advice ultimately persisted as a standard precept of antibiotic stewardship—promoted by the campaigns of leading institutions such as the CDC and the World Health Organization. However, new evidence is showing that shorter courses may be just as effective and can make more sense in terms of cost, side effects, and compliance. While clinical trials can help optimize duration, Public Health England has already opted for replacing the old “complete the course” message with “take exactly as prescribed”. Outside of the hospital—with the major exception of tuberculosis treatment—Llewelyn recommends that patients might do best to stop antibiotics when they feel better.

Three separate studies fortify the merit of antimicrobial stewardship programs (ASP)

A recent [review](#) out of Germany, spearheaded by David Bauer, has performed a meta-analysis of 32 studies on antimicrobial stewardship, conducted from 1992 to 2014. The studies cover nine million patient days from the U.S., Europe, Asia and Latin America, and is unique in its measure of the incidence of colonization or infection as the primary outcome. The authors provide clear evidence that ASP are essential to halting antibiotic resistance and should be promoted at the hospital level, not only for their cost benefit, but for their clear advantage to patient clinical outcomes. The studies evaluated such interventions as antibiotic restriction, audits of prescriber practices, antibiotic cycling, education, and implementing ASP guidelines. Key among the findings for stewardship implementation were:

- a 51% reduction in MDR gram-negative bacteria: a 56% reduction for carbapenem-resistant *Acinetobacter baumannii*, and a 29% reduction for *Pseudomonas aeruginosa*
- a 48% reduction in ESBL-producing gram-negatives
- a 37% reduction in MRSA
- a 32% reduction in *C. difficile*
- stewardship programs implemented alongside infection control measures were more effective than ASP alone (31% vs. 19% reduction in drug resistance)
- Hand hygiene was the most effective hygiene practice, especially when coupled with antibiotic cycling

The findings are considered to be an important advocacy tool that can effectively counter the stubborn pushback from naysayers, policy makers and stakeholders who continue to resist making the costly, but necessary financial investment into implementing ASP measures.

Two U.S. studies provide further evidence that antimicrobial stewardship efforts may be taking hold. The major insurer, BlueCross BlueShield [examined 173 million insurance claims](#) and found a 9% drop overall in antibiotic prescriptions, with a 16% reduction for those in children (22% in infants). Broad-spectrum antibiotic use fell by 13%. Likewise, a [study](#) published in *Clinical Infectious Diseases* has reported a 16.6% decrease in spending on antibiotics—from \$10.6 billion in 2010

to \$8.8 billion in 2015.

Slow-release charcoal may help reduce antibiotic damage to microbiome

The ingestion of oral antibiotics is known to alter the microbiome of the lower intestine—sometimes dramatically enough to cause long-term negative effects, such as *C. diff* disease. To counter these undesirable impacts, a team of scientists at the biotech company DaVolterra have undertaken a first [clinical trial](#) that tested a slow-release activated charcoal they call DAV132. Activated charcoal is a super absorbent compound that is used to remove excess drug in drug overdose cases. To prevent activated charcoal from inactivating all of an ingested antibiotic, the research team coated the charcoal particles with a covering that slowly breaks down during gut passage, allowing the charcoal to “mop up” only the excess antibiotic found in the large intestine.

The trial examined the effects of DAV132 on test subjects ingesting moxifloxacin for 5 days, compared with those consuming moxifloxacin alone. DAV 132 charcoal did not affect the antibiotic entering the bloodstream, but did reduce the amount of fecal antibiotic by ~99%. In addition, the charcoal appeared to protect close to 90% of the 250 gut bacterial species that were reduced when moxifloxacin was ingested alone. Importantly, no side effects have been observed. Pending studies will examine DAV 132 activity in sick patients taking antibiotics and will also test whether DAV 132 can reduce or prevent the emergence of antibiotic resistance. The charcoal treatment has been labelled “promising” and “a really exciting approach to protect the microbiome from antibiotics.”

Developments in antimicrobial drug therapy

Repurposing old antibiotics to beat new superbugs

Researchers at the University at Buffalo, N.Y. have [devised a triple drug cocktail](#) that show promising activity against a deadly multi-drug resistant pathogen. The superbug strain of *E. coli* that carries the mcr-1 gene has appeared a couple dozen times in the US, as well as worldwide. It is a challenging

enough adversary, but the recent emergence of *E. coli* carrying both the *mcr-1* and *ndm-5* genes present an urgent threat in terms of high-level antibiotic resistance and a potential for rapid spread. The dearth of effective antibiotics for this gene combination prompted the N.Y. team to investigate the activity of dozens of drug pairings—all including polymixin, a last-resort drug due to its potential for damage to the kidney. Combining poly B with amikacin alone ultimately produced regrowth with amikacin-resistant subpopulations; and combining it with aztreonam resulted in a persistent, but non-replicating state. However, a combination of all three drugs was able to kill the superbug in 24 hours and also prevent regrowth.

UK cancer researchers stumble on new path for finding antimicrobials

In their search for new compounds that that might be active against cancer stem cells, a University of Salford research team believes it has “accidentally invented a systematic way of creating new antibiotics which is simple, cheap and could be

very significant in the fight against superbugs.” While screening a library of compounds for anti-cancer agents that could inhibit energy production in mitochondria, the team began thinking that “if what we found inhibited mitochondria, it would also kill bacteria.” After sorting through 45,000 compounds, they identified 800 small molecule candidates, which were then narrowed down to 10, using traditional phenotype drug screening. The selected synthetic compounds inhibited five common bacterial types: *Streptococcus*, *Pseudomonas*, *E. coli*, MRSA, and the yeast pathogen, *Candida albicans*.

The Salford team named the new compounds ‘Mitochondrioscins’, which turned out to be equally or more potent than standard antibiotics. By screening drug candidates first on the mitochondria of cancer cells, the scientists acquired a systematic starting point, which had been lacking and had posed a bottleneck to antibiotic discovery for many years.

Hygiene

Neonatal study demonstrates limits of hand hygiene for controlling MRSA

During an average 9-day stay in a NICU, an infant is likely to contact hospital workers about 250 times. Utilizing a simulated neonatal intensive care unit (NICU), researchers have yielded new insights on the infant-to-infant transmission of MRSA. Hand hygiene implemented at levels of 24%, 48%, 68%, 88% and 100% corresponded to reductions in MRSA colonization of 29%, 51%, 67%, 80% and 86% respectively. While hand hygiene has long been considered the primary means for reducing pathogen transmission, the study points to the importance of other transmission routes. According to lead author Neal Goldstein, “The biggest implication is that hospitals should not just rely upon hand hygiene alone for protecting patients.” He emphasized that infection control is a multi-pronged strategy that involves all contact personnel (including visitors), protective equipment where needed, and reducing the influx of possible fomites such as cell phones, watches and jewelry.

Get Ahead of Sepsis materials launched by CDC

The theme of this year’s International Infection Prevention Week (Oct 15-21, 2017) was *antibiotic resistance*, and with it the CDC promoted new resources as part of its *Get Ahead Of Sepsis* campaign. Sepsis is a very serious condition that claims 250,000 Americans per year. The goal of the campaign is to encourage healthcare professionals and patients to get ahead of infections that can lead to sepsis and to act fast if sepsis is suspected. The campaign features new downloadable materials for healthcare professionals:

- Protect your patients from sepsis
- Be Alert. Suspect Sepsis. Save Lives

as well as two patient-directed poster/infographics:

- Protect Yourself and Your family from Sepsis
- Four Ways to Get Ahead of Sepsis

For more information about *Get Ahead of Sepsis* and to access all its materials, visit: www.cdc.gov/sepsis.

Novel door handles halt bacterial transmission

The WHO reports that actual hand hygiene compliance is seldom more than 40%. To counter this deficit, inventor Doug Olsen, inspired by watching a show on the spread of bacterial plague, has invented bacteria-killing door handle covers—created from compressed salt blocks. Resembling animal “salt licks,” the salt draws the moisture out of the cells, killing them. Testing with a one-minute exposure to 8 major pathogens has demonstrated a 90 - 100% reduction in recovery, as compared with stainless steel as a control. The “Outbreaker” door handles will become commercially available this fall.

“Smart buildings” predicted to intercept infection transmission

Writing in the U.K.’s National Health Executive, Marco-Felipe King, an infection control researcher at the University of Leeds has shared his insights on the role of “smart buildings” in infection prevention. While hand hygiene has been, and still remains, a cornerstone intervention for infection prevention, noncompliance doggedly undermines its true potential. Felipe has examined what he calls the “The Big Five” prominent routes of infection transmission: direct and indirect contact, common vehicle, droplet, and airborne transmission, and has focused his attention on understanding the interaction of the hospital building, hospital air, and staff behavior in infection prevention. Using computer simulations, Felipe and his team can now predict, not only the movement of airborne pathogens and how long they will remain suspended before landing, but also the rate of ventilation needed to mitigate infection transmission in a cost efficient manner. He predicts that in five years, “infection prevention will see smart systems such as indoor ‘weather’ forecasting at a fraction of the cost of traditional building management systems.” Such systems would employ tiny, wireless sensors in clinical areas and would relay live air quality data to a central computer, and alert staff when humidity, temperature or bio-aerosol counts pose a danger. Smart algorithms will be utilized to “forecast” areas of risk to patients, particularly those who are immune compromised or sensitive to airborne pathogens. He advocates

balancing hand hygiene efforts with antimicrobial stewardship, targeted cleaning, etc. in a total package with future smart technologies.

Diagnostics

ImmunoXpert differentiates between viral and bacterial infection

Current diagnostics are not adept at differentiating the child with a self-resolving viral illness from one with a life threatening infection. An Israeli medical diagnostics company, MeMed, has now successfully completed an external, double-blind study with its new diagnostic tool called ImmunoXpert. The study enrolled nearly 600 pediatric patients having either fever of undefined source; upper or lower respiratory tract infections; UTI; or no infection (controls). The new tool achieved 94% sensitivity in recognizing a pathogen and 90% specificity in accurately defining the resident virus. ImmunoXpert operates by measuring immune system biomarkers found in the blood. These identifications are coupled with machine learning algorithms—identity patterns created by certain infections. One aim of the new diagnostic is to reduce costly antibiotic mismanagement that follows misdiagnosis. With financial support from the U.S. Dept. of Defense, the research team aims to develop an easy to use, rapid point-of-care platform that can be utilized globally in many diverse clinical settings.

Super fast diagnostics reduce susceptibility testing times

Traditional antimicrobial susceptibility testing generally requires 1-2 days for a determination. Three independent research teams are reporting novel methods for reducing this time down to a few hours or less. All operate on short-term exposure to an antibiotic, but differ in their means of determining the cellular reaction. All methods are aimed at reducing unnecessary antibiotic use by quickly identifying the most effective antibiotic for treatment.

□ One Harvard-based team is using arrays of microwells that confine a few bacterial cells in a small area to precisely

monitor their growth against different antibiotic classes. The MIC can be determined in under three hours and has the potential for development into a sensitive and robust hospital and laboratory tool.

□ In Sweden, Uppsala University scientists have developed a technique for observing whether individual cells actually grow in the presence of an antibiotic. Their device utilizes a new microflow plastic chip to capture, grow and observe bacterial cells at the single cell level. Astrego AB is developing an automated, user-friendly version of the device for UTI diagnosis in hospitals and health centers within 2 years.

□ A third diagnostic, developed by a Caltech team, also focuses on urine and compares antibiotic-exposed (15 minutes) and unexposed samples. Cells are then lysed and run through two processes—dLAMP* and SlipChip—which together, replicate specific DNA markers and image them as fluorescent spots. Antibiotic-susceptible cells will replicate their DNA less well under antibiotic exposure, thereby producing fewer DNA markers. The test had a 95% accuracy rate on UTI samples, achieved in 30 minutes, and is being tried on other infectious bacteria and sample types.

**digital real-time loop-mediated isothermal amplification*

Epidemiology

Excess antibiotic use found among asthma patients

According to a study of two primary care databases, conducted between 2000 and 2014 in the Netherlands and the U.K., children diagnosed with asthma received more antibiotic prescriptions than those without an asthma diagnosis. For children with asthma, the prescribing rates were 19.7% (Netherlands) and 37.4% (U.K.) In those without asthma, the rates were 12.6% (Netherlands) and 25% (U.K.)

The study data revealed that antibiotics were largely prescribed for either asthma exacerbations or bronchitis—both of which are commonly caused by a virus, not a bacterium. The most commonly used antibiotic was amoxicillin. Study author, Esma Baan noted that, “Asthma is a common and ongoing condition and it has symptoms that could be mistaken for a respiratory

tract infection.” However, bacterial infections are seldom involved in deteriorating asthma, and both international and national guidelines clearly indicate that antibiotics are contraindicated for this condition. Interestingly, The Netherlands has one of the lowest antibiotic prescribing rates in the world, but was still found to use these drugs inappropriately in the asthma population.

New reports solidify link between antibiotic consumption and resistant infection

A second JACRA Report,* resulting from the close collaboration of three EU agencies, has confirmed the link between antimicrobial consumption and antimicrobial resistance in both humans and animals. The conclusions mirror those of an earlier 2015 report, but present a more sophisticated analysis due to better quality data. For the first time, the report employed estimated data on antimicrobial consumption in pigs and poultry. Overall, the average antimicrobial consumption remained higher in animals than humans (152 vs. 124 mg/kg, but in 18 of the 28 countries, the reverse was true, showing important variations across EU countries. They found that polymyxins (including colistin), which are increasingly used in hospitals for MDR infections, are also used widely in animals. In contrast, the 2nd and 3rd generation cephalosporins are most often used in humans.

Importantly, the report notes a statistically significant correlation between antimicrobial consumption and antibiotic resistance for the following:

- 1) fluoroquinolones and *E. coli* in both animals and humans;
- 2) 3rd and 4th- generation cephalosporins and *E. coli* in humans; and
- 3) tetracyclines and polymyxins and *E. coli* in animals.

In a separate publication, The PEW Charitable Trusts have released the results of a systematic evaluation of over 100 studies worldwide that allow examination of the steps in the pathway from antimicrobial use in farm animals to a human public health risk. The study examined four variables:

**The Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) was issued by the European Food Safety Authority, The European Medicines Agency and the European Center for Disease Prevention and Control*

- Antimicrobial drug use on the farm;
- The resulting risk of emerging antibiotic resistance;
- The risk of infection arising from resistant bacteria; and
- Excess morbidity and mortality from antibiotic resistance

The authors conclude that, “...there is no doubt that antimicrobial use on farms or feedlots contribute to the problem of antimicrobial resistance.” They concede that exact quantitation is still challenging and data gaps remain; however, their findings reinforce the need to act quickly to strictly confine antibiotic exposure in food animals to those instances where it is essential to the animals’ health and well-being.

Two studies shed new light on emergence of antibiotic-resistant mutants

Researchers at the University of Manchester have made important observations regarding bacterial density and the rise of resistant strains. The research team, headed by Chris Knight, found that mutation rates vary within a microbe’s environment: the more sparsely populated a bacterial niche, the more likely mutations will arise, resulting in antibiotic-resistant strains. Denser microbial communities produced fewer resistant strains. The observation – called “density-associated mutation-rate plasticity” or DAMP – arose from analysis of 500 different mutation measurements from 70 years of data. The authors claim that DAMP affects the course of evolution, which can lead to a better understanding of antibiotic resistance and how it arises in the first place. The authors suggest that their findings may lead to a clinical manipulation of DAMP in order to slow the pace of evolving antibiotic resistance.

In another study published in *Genome Biology*, scientists have shed insights on the early emergence of resistance to the antibiotic methicillin. It has long been accepted that use of methicillin drove the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA). Now, scientists from the U.K. have demonstrated that it was the widespread use of penicillin in the previous years that drove the resistance. The research team, led by Matthew Holden, determined that the *mecA* gene (which codes for methicillin resistance via production of penicillin-binding protein 2a, or PBP2a) entered *Staph aureus* in the mid-1940s – selected by the use of penicillin. Methicillin was

introduced in 1959 to circumvent penicillin resistance, and in 1961, methicillin-resistant strains began emerging and spread widely — creating multiple MRSA lineages in the following five decades.

The discovery was made by sequencing over 200 historic *S. aureus* strains collected in Europe between 1960 and 1989. The sequences also revealed resistance genes for multiple other antibiotics, as well as genes coding for diminished susceptibility to disinfectants. Regarding the significance of the finding, Professor Holden commented, “It shows that new drugs...can be rendered ineffective by unrecognized, pre-existing adaptations in the bacterial population.” The findings emphasize the old adage: “forewarned is forearmed”; effective surveillance combined with sequencing is needed to pre-empt resistance emergence.

Report updates *C. diff* stats in U.S.

Clostridium difficile is the most common healthcare-associated infection, infecting half a million people and taking tens of thousands of lives per year at a cost of \$5 billion annually. It is highly associated with antibiotic consumption and often recurs after treatment—anywhere from 13-50% of patients have at least one recurrence following the first episode. An Annals of Internal Medicine report (July 2017) has updated the statistics on *C. difficile* infection (CDI) and its multiply resistant forms (mrCDI) on commercially insured U.S. patients. Between 2001 and 2012, the annual incidence of CDI per 1000 person-years increased 42.7%, and mrCDI increased a disproportionate 188.8%. Those with mrCDI were more likely to be older, female, and to have used antibiotics, proton-pump inhibitors or corticosteroids within 3 months of diagnosis. Chronic kidney disease and nursing home residency were also risk factors.

The new study found that 1 out of every 5 patients with a healthcare-associated *C. difficile* infection experienced a recurrence of the infection and 1 out of every 11 patients aged 65 or older with a healthcare-associated *C. difficile* infection died within 30 days of diagnosis.



“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.

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APUA global chapter network of local resources & expertise



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