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Evaluating Antibiotic Resistance, Residues and Revitalization

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Momentum Builds for Action Against Antimicrobial Resistance (AMR): A Timeline

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| July 2014 | UK Commissions Review on Antimicrobial Resistance |
| Mar 2015 | US president Obama establishes Presidential Advisory Council on Combating Antibiotic-resistance Bacteria (P-CARB) |
| Jan 2016 | World Economic Forum: the pharmaceutical, biotech and diagnostics industries issue declaration to combat AMR |
| May 2016 | <ul style="list-style-type: none">WHO's <i>Global Action Plan</i> commits 194 member nations to producing national control plans by 2017The G7 industrialized nations make MAR resistance an international priority |
| Sept 2016 | <ul style="list-style-type: none">The G20 developing nations commit to reducing AMRUN High-Level Meeting ratifies political declaration for the global, multisectoral addressing of AMR9 found organizations launch the Conscience of Antimicrobial Resistance Accountability (CARA) |



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Antibiotics and Antibiotic Resistance All Around Us

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Today, we are experiencing a boom in news on the antibiotic resistance crisis. APUA was founded 35 years ago in response to emerging and rising resistance. In 1994, the notable magazines *Time* and *Newsweek* devoted their covers to the growing resistance threat. But it was not until the current century that a rather curious surge in interest occurred—fueled by the WHO, the USA and EU CDCs, and the White House, among others (a UN General Assembly high-level meeting on antibiotics was scheduled this September¹). In particular, two multi-resistant organisms triggered this response: first, the so-called "methicillin resistant *Staphylococcus aureus*" (MRSA), especially in the USA; and secondly, the "carbapenem-resistant enterobacteria" (CRE). More recently, the discovery of a new colistin resistance determinant, although not yet linked to clinical failure of this "last resort" antibiotic, set a scary perspective. While useful in acting as triggers of global responses, these infamous organisms obscure the much graver background of gradually increasing resistance that is emerging in everyday pathogens, and has led to an estimated 700,000 annual deaths worldwide.² Furthermore, the causes and consequences of resistance escape the clinical setting. Clinical abuse of antibiotics is not the only – perhaps not even the most important – cause of resistance; and increased morbidity and mortality of infections are not the only consequences.

Clinical abuse of antibiotics is rampant. Antibiotics used when not needed, coupled with poor choices of drug or dosing, amount to around 50% of medical prescriptions. Ubiquitous

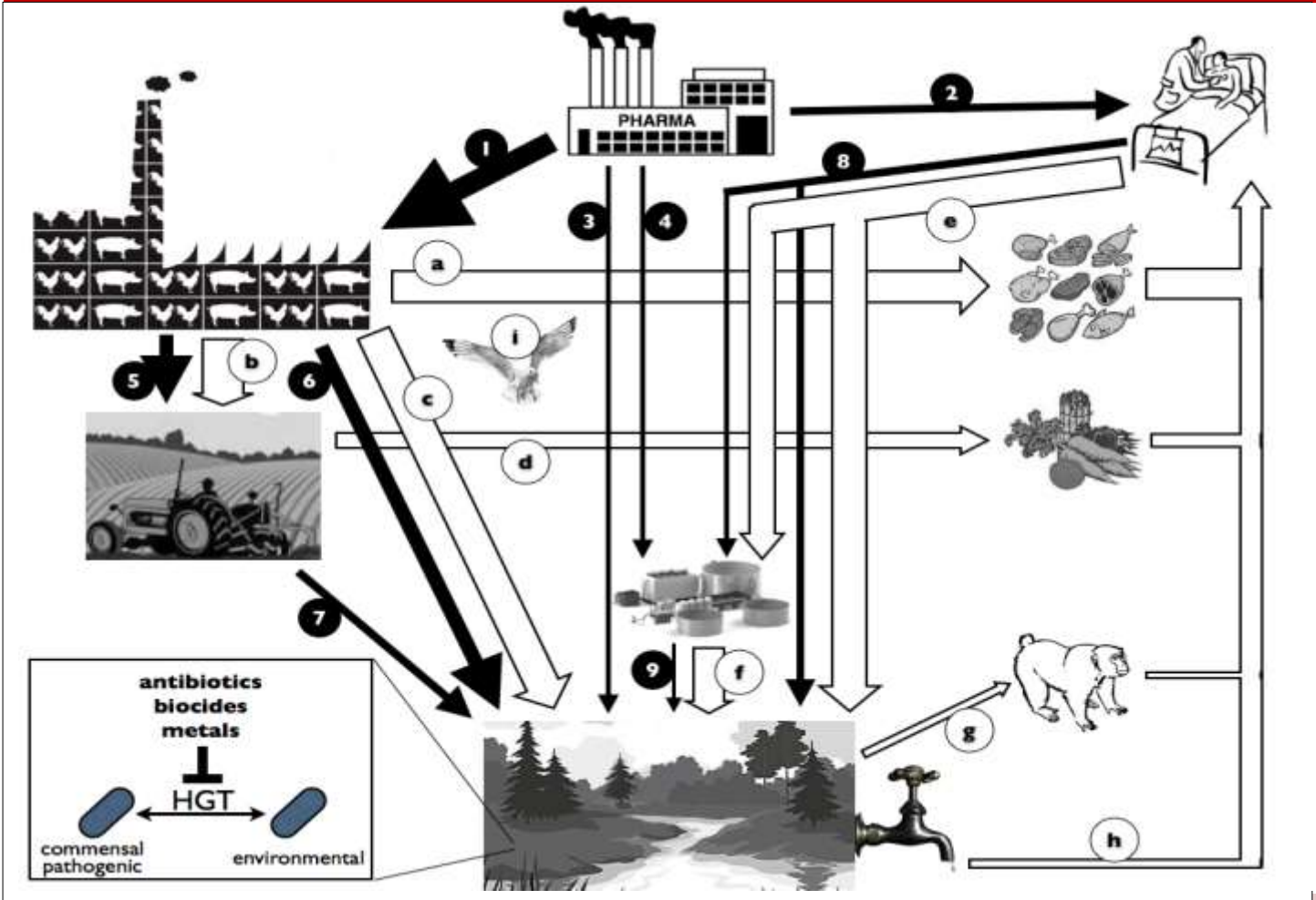
self-prescriptions, ranging from 3% in some European countries, to 100% in a couple of African countries³ (a 35% crude average), may be wrong much more often; but even considering *all* self-prescriptions to be wrong, such abuse would amount to about the same as wrong medical prescriptions. Reduction in the clinical abuse of antibiotics is urgently and globally needed, both by improving medical prescriptions and suppressing self-prescription. Nonetheless, the overall impact will be almost negligible in terms of antibiotic amounts. Approximately 70% (on weight basis) of all antibiotics produced in the U.S. are used in agriculture.

Even if all self-prescription and wrong medical usage is reduced to zero, there would only be a 20% reduction in total antibiotic use (25% at best, if considering a 63/37 ratio of agricultural/clinical antibiotic use worldwide).⁴ To significantly curb the growing resistance trend, a much more substantial reduction in antibiotic usage is needed.

“In the end, most of the approximately 100,000 tons of antibiotics produced annually worldwide end up polluting the environment.”

Except for the therapeutic use of antibiotics on sick animals, all other agricultural usage is morally indefensible. Jeopardizing the health and lives of people to save money in the growing of food animals is simply unacceptable. Resistant organisms are selected in those food animals that ultimately become our foodstuffs and reach our kitchens, causing resistant infections, and/or mobilizing resistance genes to other pathogenic bacteria. But that is just the “tip of the iceberg”. Tons of manure from antibiotic-fed animals (containing active antibiotics and resistant bacteria) are spread as fertilizer, polluting soils and vegetables; and thousands of pounds of

Figure 1. Antibiotics and Resistance All Around Us: A Graphic



(Antibiotics - filled arrows; resistant bacteria - open arrows.) Pharmaceutical companies worldwide produce ~100,000 tons of antibiotics per year. Most (63-70%) are used in agriculture and aquaculture (1), while only 30-37% are used in humans (2)—both hospitalized or as outpatients. A small amount of active by-products is released to wastewater, either directly into the environment (3) or to treatment plants (4). Unmetabolized antibiotics are excreted by antibiotic-fed animals, and end up in manure used as fertilizer (5) or as liquid or solid waste dumped into the environment (6). Antibiotics from manure leach into deeper soils and water bodies (7). Unmetabolized antibiotics are also excreted by human patients. In cities, where the majority now live, these drugs end up in the sewage, (8) which is dumped directly into water bodies (in developing countries) or into wastewater treatment plants. While few antibiotics survive the treatment processes, some do and are released into water bodies, or persist within sludges that are also dumped (9) or used as fertilizer. The bacterial aspects are also complex. Resistant bacteria are selected within antibiotic-fed animals and contaminate their meat (a), while also being released in their feces and spread as fertilizer (b) or dumped along with other waste into the environment (c). Vegetables grown on manured soils (d) also carry resistant bacteria. People themselves, both, treated and untreated, release enormous amounts of resistant bacteria within feces, that end up in the sewage of cities (e), which is mostly dumped directly, or fed into wastewater treatment plants. While wastewater treatment reduces the overall bacterial load, surviving organisms are the result of intense gene exchange within sludges under many selective pressures, making them particularly resistant (f). Resistant bacteria in soils and waters colonize wildlife (g), and some can even find their way into tap water (h). Birds (i) may play a particular role in dispersing resistant bacteria since they feed in many of these different settings and are airborne. The result of releasing bacteria that have been under the effects of high concentrations of antibiotics is not only the direct risk of acquiring a resistant infection. Commensal and pathogenic bacteria (box, bottom left)—loaded loaded with resistance, virulence and mobility genes—come into close contact with environmental bacteria that are often innocuous, but carry ancient resistance genes. Horizontal gene transfer (HGT) can easily ensue, under the selective pressure of antibiotics, other biocides and heavy metals, that are released into the environment due to human activities.

antibiotics are directly applied to water bodies used for aquaculture. This is of course in addition to the un-metabolized antibiotics released by treated patients; the disposal of unused antibiotic pills and solutions from homes and hospitals; and the release of antibiotic by-products by pharmaceutical factories—all going into wastewater and landfills. In the end, most of the approximately 100,000 tons of antibiotics produced annually worldwide end up polluting the environment.⁴ At dumping sites, antibiotics reach concentrations above clinical MICs (*e.g.*, in hospital sewage, or in rivers downstream of pharmaceutical factories). They subsequently dilute to sub-MIC levels, which are generally disregarded. However, such “sub-inhibitory” concentrations can still exert effects upon soil and water microbiotas, either alone or along with other human-released biocides. For example, herbicides that lower the bacterial susceptibility to some antibiotics⁵ could potentially turn sub-MIC quantities into effective selective pressures. All this environmental disturbance can select for ancient resistance genes in environmental bacteria and promote their mobilization into pathogens. This is presumably what happened with the CTX-M extended-spectrum beta-lactamases and the *qnr* plasmid-bearing quinolone resistance genes. Environmental contaminants can also alter the composition of soil microbiota in unpredictable ways and could affect many geo-biological processes that depend upon soil bacteria.⁴

Along with antibiotics, resistant bacteria are released at staggering amounts into all environments, urban and rural. Resistant bacteria may often also bear dangerous mobile genetic elements (*i.e.*, plasmids, ICEs [integrative and conjugative elements], transposons, integrons, gene cassettes, etc.), which allow the transfer of resistance genes horizontally to other microbes,—enabling the mobilization of ancient resistance determinants. Resistant bacteria that are selected within treated patients and within antibiotic-fed animals are released in their feces into water bodies, either directly (as in most rural and developing-country settings), or after the particularly pernicious process of concentration, gene-rearrangement and selection that occurs at wastewater treatment plants.⁴ Open-air fecalism and sewage-disposal

contributes to the significant levels of resistant bacteria from urban dust in developing countries. Likewise, airborne animals, especially birds, can mobilize resistant bacteria, including transport from countries that use antibiotics agriculturally into those that have banned such practices.⁶ It can be argued that the overall impact of such a release is irrelevant, since resistant bacteria are already much more abundant in clinical settings, and antibiotics would not play a role in a hypothetical outbreak caused by resistant organisms in wild animals. But the ecological impact of the release of resistance and mobility traits into soil and aquatic microbiotas that are also tainted with antibiotics, other biocides and heavy metals, is nearly impossible to assess. In addition, resistant bacteria are frequently reported in wildlife. The health impact upon affected wild animals, and the risk of concocting a modified strain capable of infecting humans and of resisting multiple antibiotics should not be overlooked.⁴

One of the many measures proposed to confront the resistance problem is to create or increase public awareness.^{1,7} But this must go far beyond the notions of restraining the urge to get an antibiotic prescription from a physician, and avoiding self-prescription. It is vital that people realize the many aspects of this serious health threat so that they can organize and exert pressure to stop the global abuse of antibiotics.⁸ Governments worldwide have been largely negligent, and international organizations (*e.g.*, UN, WHO, FAO) that depend on government cooperation have their hands tied. Only the organized response of societies worldwide can act against the trans-national threat posed by antibiotic resistant pathogens.

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Why Limit Antibiotic Pollution? The Role of Environmental Selection in Antibiotic Resistance Development

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Antibiotic resistance is estimated to cause hundreds of thousands of deaths every year.¹ At the same time, new types of antibiotic resistance mechanisms continue to be discovered among both pathogenic and harmless bacteria.^{2,3} This development points towards the existence of a large source of resistance factors outside of the human microbiome – the environmental bacteria present virtually everywhere on earth.^{4,5} Although many resistance genes already have emerged in pathogens, their specific origin and the circumstances that favored their transition are still largely unclear.⁶ Most likely, the most critical factor in the emergence, mobilization and spread of novel resistance genes to human and animal pathogens is a selection pressure from antibiotics.⁷ Bacteria in the human and animal gut flora are frequently exposed to sufficiently high concentrations of antibiotics to select for resistant strains. However, an often overlooked aspect is that the taxonomic diversity of the gut flora, and hence the available source of potential novel resistance factors, is tiny compared to that of environmental microbial communities. Research over the past decades indicates that antibiotic residues also reach the environment and, in some cases, select for resistance. Therefore, a fundamental understanding of where selective conditions for antibiotic resistance exist is crucial in order to develop comprehensive mitigation strategies that will avoid or delay future resistance development associated with the environmental resistome.⁸

Defining selective concentrations of antibiotics

Antibiotics can exert selection for resistance at concentrations below those that completely inhibit bacterial growth.⁹ To

identify environments that may act as spawning grounds for resistance, we must define the concentrations of antibiotics that can drive resistance development. Several approaches have been explored to determine these minimal selective concentrations,⁷ ranging from biologically simplistic, but very precise competition experiments between resistant and non-resistant strains,⁹ to experimental setups aimed at capturing the complex interplay of full-scale microbial communities.¹⁰ From an ecological standpoint, methods designed to quantify the levels

Box I. Predicting “no-effect concentrations” for antibiotics

- ◆ The lowest minimal inhibitory concentration (MIC) for each species-antibiotic combination in EUCAST was collected. For some antibiotics, the number of tested species was small.
- ◆ The potential bias caused by low species coverage on the observed lowest MICs was estimated by sub-sampling MIC data for the antibiotics with many tested species. This sub-sampling data was used to predict size-adjusted lowest MICs.
- ◆ An assessment factor of 10 was then applied to account for that minimal selective concentrations by necessity would be lower than the MICs, arriving at predicted “no-effect concentrations” (PNECs) for 111 antibiotics in total.

Note: MICs and PNECs in Table 1 are rounded down to the closest number on the EUCAST testing scale. We also compared each PNEC to the highest concentration reported in effluents from sewage treatment plants.¹⁵

of an antibiotic that promote resistance in complex communities should better capture the effects of sub-inhibitory concentrations found in real environments, such as wastewater treatment plants and their recipients. However, both competition experiments and microcosm investigations of complex communities are labor-intensive. Nonetheless, a reference framework for selective concentrations of antibiotics is urgently needed.¹¹ Therefore, we took advantage of the EUCAST database¹² containing minimal inhibitory concentrations for a large range of bacteria (170 species) and used it to predict the estimated “no-effect” concentrations for 111 antibiotics (Box 1; Table 1).¹³ The estimated “no-effect” concentrations are based on the assumption that an antibiotic concentration that inhibits growth of certain bacterial species will also be selective, since it enables non-susceptible strains to outcompete sensitive ones – at least in some communities. The predicted no-effect concentration for tetracycline has subsequently been validated experimentally in complex

aquatic biofilms and shown to be in the expected range¹⁰ (Figure 1). Many of the predicted no-effect concentrations for resistance selection are substantially below those expected to have ecotoxicological effects on other organisms.¹³

Identifying environments at risk for selection of resistance factors

With a framework of no-effect concentrations for resistance selection in place, we are now able to identify environments that bear the potential to confront bacteria with selective conditions. One environment that often has been suggested as a “hotspot” for resistance development is the sewage treatment plant.¹⁴ When we apply the above framework, we can see that measured concentrations of antibiotics in untreated sewage influent often barely attain predicted no-effect concentrations, and only do so for a few antibiotics.^{13,15} Furthermore, in a recent study of ours where concentrations of ciprofloxacin and tetracycline in influent water were slightly

Table 1. Estimated minimal selection concentration boundaries and predicted no-effect concentrations for 26 commonly used antibiotics

Antibiotic	Antibiotic class	N ¹	Covered genera (families)	Observed lowest MIC (µg/L)	Size-adjusted predicted lowest MIC (µg/L) ²	PNEC (incl. assessment factor) (µg/L)	STP Effluent conc. (µg/L) ³
Gentamicin	Aminoglycosides	68	27 (14)	16	16	1	1.3
Tobramycin	Aminoglycosides	31	15 (8)	16	8	1	
Co-trimoxazole	Antifolate combinations	36	22 (13)	8	4	0.5	
Ertapenem	Carbapenems	36	20 (12)	2	1	0.125	
Cefalexin	Cephalosporins (1st gen.)	10	7 (5)	250	32	4	1.8
Cefaclor	Cephalosporins (2nd gen.)	11	7 (6)	32	8	0.5	1.8
Cefdinir	Cephalosporins (3rd gen.)	5	4 (4)	32	2	0.25	
Benzylpenicillin (G)	Narrow-spectrum penicillins	47	12 (11)	4	4	0.25	
Phenoxymethylpenicillin (V)	Narrow-spectrum penicillins	8	5 (5)	4	0.5	0.064	2
Amoxicillin	Extended spectrum penicillins	29	19 (12)	4	2	0.25	0.05
Ampicillin	Extended spectrum penicillins	64	25 (15)	4	4	0.25	0.126
Vancomycin	Glycopeptides	42	10 (9)	125	125	8	0.04
Daptomycin	Lipopeptide	16	6 (6)	32	8	1	
Azithromycin	Macrolides	12	6 (6)	16	4	0.25	0.38
Clarithromycin	Macrolides	15	10 (10)	8	2	0.25	0.61
Erythromycin	Macrolides	39	14 (13)	16	8	1	0.62
Linezolid	Oxazolidinones	29	9 (9)	125	64	8	
Chloramphenicol	Amphenicols	29	18 (11)	125	64	8	
Colistin	Polypeptides	16	10 (4)	64	16	2	
Ciprofloxacin	Fluoroquinolones (2nd gen.)	70	29 (18)	2	1	0.064	0.742
Levofloxacin	Fluoroquinolones (3rd gen.)	43	24 (16)	4	4	0.25	
Moxifloxacin	Fluoroquinolones (4th gen.)	53	21 (14)	2	2	0.125	0.017
Rifampicin	Rifamycins	19	12 (12)	2	0.5	0.064	
Tigecycline	Glycylcyclines	54	26 (16)	16	16	1	
Doxycycline	Tetracyclines	29	20 (11)	32	16	2	0.915
Tetracycline	Tetracyclines	66	30 (18)	16	16	1	0.62

Notes: 1. These numbers correspond to the number of different species present in EUCAST that could be matched to a valid species name in the SILVA database. 2. The size-adjusted predicted lowest MIC correspond to the estimated upper boundary for the minimal selective concentrations. 3. The highest concentration observed in effluents from conventional sewage treatment plants, as reported by Michael et al.¹⁵

above the predicted no-effect concentrations, no consistent enrichment of genes encoding resistance against any class of antibiotics was observed during the treatment process.¹⁶ Taken together, the evidence for resistance selection in sewage treatment plants is still limited, but at the same time, many of the studies, including ours, have shortcomings that limit interpretation. This is partly because we know little about how mixtures of antibiotics act, but also because of the immense changes in species composition that occur in sewage treatment plants due to various other factors that may mask the effects of direct antibiotic selection. More comprehensive culture-based studies on changes in resistant/non-resistant strains within species are therefore required, both in sewage treatment plants and in receiving waters.

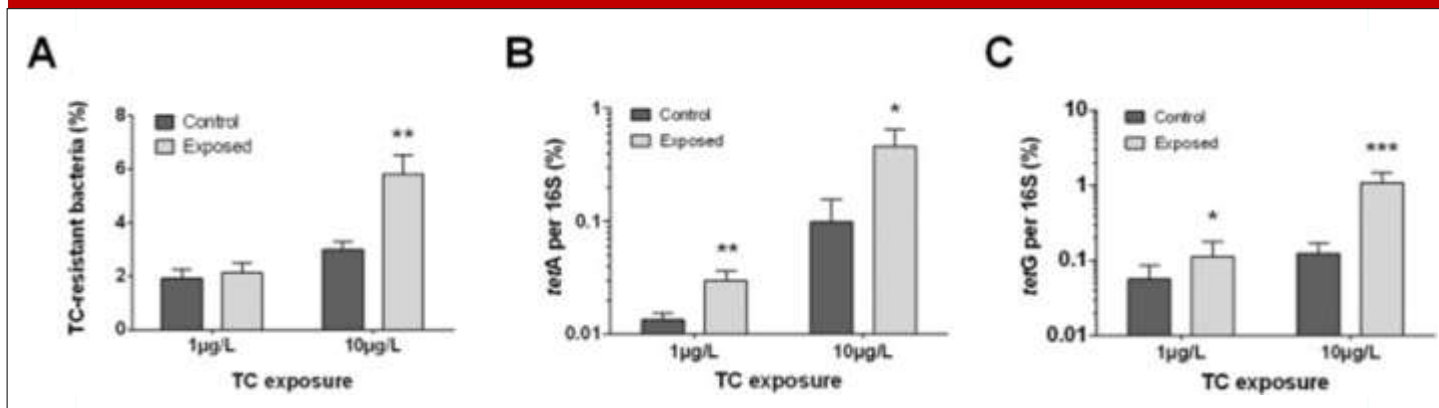
The conditions in sewage treatment plants can be contrasted with those in environments that are subjected to pollution from antibiotic manufacturing. In the latter, substantially higher concentrations of antibiotics have repeatedly been measured,¹⁷ sometimes greatly exceeding the therapeutic concentrations found in human blood during treatment.¹⁸ In several instances, this has been associated with high abundance of resistance genes and – perhaps even more

worryingly – a vast diversity of resistance mechanisms, along with genes responsible for horizontal gene transfer.^{19,20}

Developing mitigation strategies

The WHO acknowledges that mitigations to limit resistance development should employ a One-Health approach that also includes the external environment.²¹ It seems reasonable that priority should be given to measures that would be relatively straightforward to enforce, are associated with limited cost, and carry a large potential impact. Accordingly, the recent O'Neill review on antimicrobial resistance¹ highlights the urgent need to take control of antibiotic pollution from manufacturing, beginning with the discharge limits we have published.¹³ Such discharge limits could be applied not only in the form of local regulations, but also during procurement by major buyers of antimicrobials.²² We also believe there is a need for action in environments contaminated by antibiotic residues from both animal farming and human habitation.²³ However, the overall risks associated with transmission of already-resistant pathogens may very well exceed the risk associated with residues of selective agents in these environments. Both of these different risk scenarios are important to consider when taking actions to manage

Figure 1. Minimal selective concentrations for tetracycline



Results of two experiments with tetracycline (TC; 1 and 10 µg/L versus matched controls) aiming at determining minimal selective concentrations for both phenotypic and genotypic resistance endpoints. (A) Percent TC-resistant bacteria as determined by comparing the number of colony forming units on R2A plates with or without TC (20 µg/mL). A significant increase was demonstrated for 10 µg/L ($p = 0.0045$) but not for 1 µg/L ($p = 0.34$). (B) Relative changes in *tetA* levels as determined by quantitative PCR (1 µg/L, $p = 0.005$; 10 µg/L, $p = 0.017$) (C) Relative changes in *tetG* levels as determined by quantitative PCR (1 µg/L, $p = 0.026$; 10 µg/L, $p = 9.95 \times 10^{-7}$). One-tailed Student's t-tests were performed using percentages (A) or the log₂ values of the relative difference in gene-levels between *tet*-genes and 16S rRNA (B,C). Reprinted from Science of the Total Environment,¹⁰ copyright (2016), with permission from Elsevier.

discharges. While installation of advanced sewage treatment technologies may certainly be warranted in specific situations, more is likely to be gained globally in terms of reduced resistance risks by implementing basic sewage treatment systems in low-income regions of the world.²⁴

Some knowledge gaps to address

The predicted no-effect concentrations for antibiotic resistance selection are not thought to be set in stone.¹³ Instead, they should ideally be complemented with experimental data as it becomes available. Furthermore, other effects of sub-lethal antibiotic levels, e.g., those exerted on horizontal gene transfer,^{25,26} are only starting to be elucidated. We also know little about the potential contribution of co-selective agents, such as biocides and metals, on antibiotic resistance development,²⁷ or how mixtures of antibiotics should be assessed.²⁸ Still, the urgency of addressing the accelerating antibiotic resistance threat makes it overly clear that we cannot let these knowledge gaps delay the initiation of relevant mitigation efforts in areas where improvements can be made relatively easily.

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Optimizing the Use of Old Antibiotics— A Global Health Agenda

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Antibiotic resistance is recognized as one of the global challenges that can only be tackled by a global comprehensive response. The need to intensify joint international efforts is highlighted in the current high-level initiatives and will be discussed at such important events as the United Nations General Assembly and the World Health Summit in September and October 2016, respectively. All the ongoing initiatives recognize the multifactorial complex problem and the need for multiple simultaneous actions, including surveillance of antibiotic use and resistance, infection control, stewardship, improved use of antibacterial therapies, strengthening research and R&D pipelines, and control of agricultural use and environmental pollution. Most of the suggested policies include the call to optimize the use of current antibiotics. As the Review on Antimicrobial Resistance report phrased it, “We need to use existing antimicrobials better”.

Why Revive Old Antibiotics?

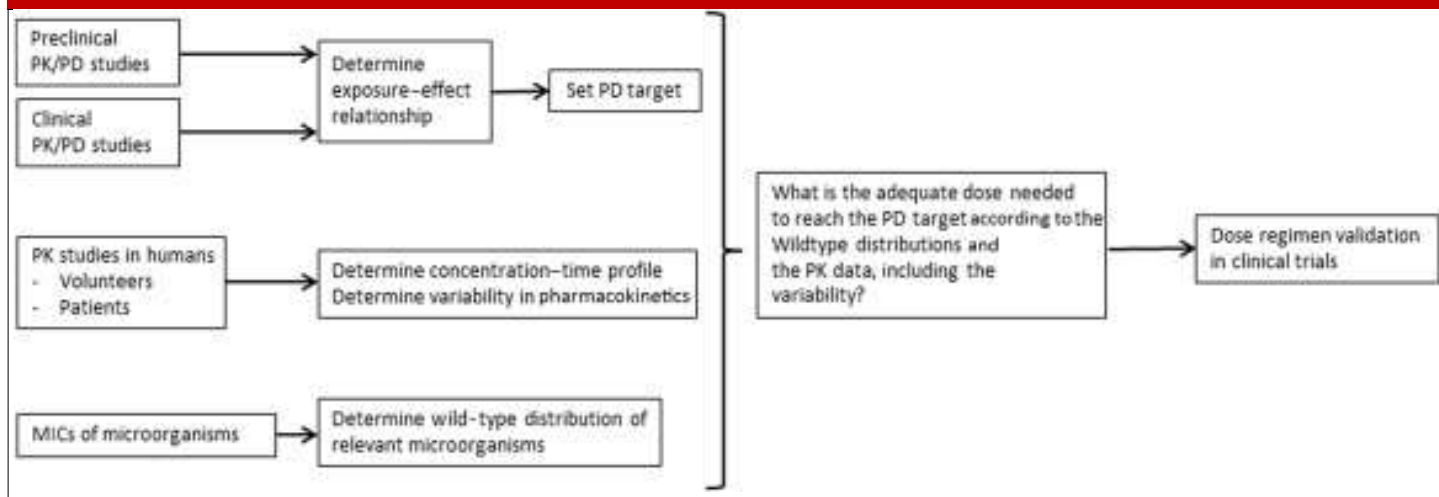
From the public health perspective and the realities of daily clinical practice, old antibiotics may not always be used to their full potential. Individualized dosing regimens—based on the pharmacokinetics (PK) in the individual patient in relation to the pharmacodynamic (PD) characteristics of the infecting pathogen—are increasing the probability of eliminating an infectious organism. The past 25 years have witnessed marked insights into how antibiotics act on bacteria and how they behave in patients. Translating research into medical practice is still ongoing. Older antibiotics are not merely the workhorses of modern medicine. Some of them – though forgotten or neglected for decades – have retained their activity against most multidrug-resistant (MDR) bacteria and may expand therapeutic options in such situations. Some of these older antibiotics

have been revived after decades of disuse and are increasingly employed in clinical situations as described below.

In the community and in extended care facilities, a typical example is the revival of old antibiotics as quinolone-sparing options for the treatment of urinary tract infections (UTI). The most common pathogen in community-acquired UTIs is *E. coli*—with an increasing trend towards multidrug resistance (MDR) in many parts of the world. Such bacteria are usually producing extended-spectrum beta-lactamases (ESBL) and are therefore resistant to aminopenicillins and cephalosporins and also frequently co-resistant to quinolones and other antibiotics. In countries with low rates of MDR bacteria, first-line alternative quinolone-sparing regimens may alleviate the selection pressure that is exerting resistance against quinolones and other co-resistant antibiotics such as cephalosporins. In countries with very high rates of MDR enterobacteria, *E. coli* and *Klebsiella pneumonia* are recognized as important causes of hard-to-treat urinary tract infections, with few oral treatment options available. Old antibiotics that are increasingly used in these situations are fosfomycin-trometamol and nitrofurantoin. Due to their different mode of action, there is no cross-resistance to other common antibiotic classes. Pivmecillinam is an old penicillin with activity against enterobacteria and increased stability against beta-lactamases. This drug is not widely available, but may also be an alternative in specific situations.

In hospitals, the escalating prevalence of ESBL-producing enterobacteria bearing co-resistance to other antibacterial drug classes requires carbapenem-sparing options to limit the heavy selection pressure and emergence of carbapenem resistance. Where available, antibiotics such as fosfomycin iv or temocil-

Figure 1. Concise diagram of data needed for (re)development of an antibiotic



PD - pharmacodynamic; PK- pharmacokinetic.

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lin are increasingly being revived to treat ESBL-producing bacteria.

Severe hospital-acquired infections are increasingly caused by carbapenem-resistant gram-negative bacteria, which are commonly extensively drug resistant (XDR) and only susceptible to colistin and sometimes tigecycline, fosfomycin and an aminoglycoside. Colistin has undergone a substantial resurgence in its use as a last-line treatment over the last decade. At the 1st and 2nd International Conference on Polymyxins (2013 and 2015), a set of key objectives was developed to explore the factors affecting the safe and effective use of polymyxins, present new data, identify the gaps in knowledge, and set priorities for future research. It remains to be seen whether recently approved new beta-lactamase inhibitor combinations (ceftolozane/tazobactam and ceftazidime/avibactam) can become affordable and partly replace colistin without being limited by the rapid spread of pre-existing resistances.

Optimizing the Use of Old Antibiotics

The above-mentioned antibiotics first became available during the 1950s – 1970s but were never developed using the current structured process for drug assessment and regulatory approval. As a consequence, revived old antibiotics are being prescribed using the limited knowledge generated 50-70 years ago. The official product information and labels refer to origi-

nal data that may be insufficient or simply wrong. This is especially true for PK data and dosing recommendations in difficult-to-treat patient groups. Using antibiotics based on the knowledge and data generated decades ago is unacceptable in modern medicine.

The lack of up-to-date evidence underscores the importance of “re-developing” these drugs in academic and clinical settings and filling the most vital knowledge gaps (Fig. 1; Table 1). Substantial progress has been made in key areas over the last 20 years of developing newer antibiotics. These include bioanalytical methods for accurate quantification of antibiotic in biological fluids; better understanding of antimicrobial PK/PD, including exposure-effect and emergence of resistance relationships; dose-finding approaches and optimizing dosing regimens, including individualization; susceptibility breakpoint setting; safety assessment; and evidence-based therapy based on randomized controlled clinical trials in today’s patient population and current environment of antibiotic resistance. These are also the most obvious knowledge gaps for revived antibiotics. The most advanced revived antibiotic is colistin, which is being “re-developed” in investigator-initiated clinical studies supported by public funding, albeit not based on a collaborative and structured process. New methods and knowledge have superseded the original information, especially in the areas of PK/PD, analytical assays, dosing optimization (including in

special patient populations) toxicity and emergence of resistance in relation to drug exposure.

Challenges Remain

Strategies are urgently needed to “re-develop” these drugs in a structured and coordinated way using modern standards, integrating new knowledge into regulatory frameworks, and communicating the knowledge from research bench to bedside.

A globally coordinated process of funding the necessary studies to “re-develop” old antibiotics would safe-guard our resources and increase the relevance of results. Integrating new knowledge into product information and labels in the absence of an originator is still a challenge for regulatory agencies. The European Medicines Agency (EMA) has processes in place to harmonize and update the product information. Colistin exemplifies this process as new information accumulates that changes the way this antibiotic is used. An often overlooked consequence of outdated labels is their impact on the development of new antibiotics. Comparing an old antibiotic based on a registered inferior dosing regimen with a new antibiotic using an optimized dosing regimen based on prior experience of this class may lead to misleading conclusions, thus overestimating the efficacy of a new antibiotic.

Sharing and communicating new knowledge of old drugs to the medical community remains a global challenge. Current information channels are conventional, narrow, slow and are not sufficient. As antibiotic resistance is emerging and spreading rapidly, new models for rapid knowledge dissemination are required. Ultimately, issuing treatment guidelines based on the findings of new studies and communicating those findings to the medical community ensures the translation of knowledge to the bedside.

Revived antibiotics are typically not included in international resistance surveillance programs nor in the routine panels of automated antibiotic susceptibility testing systems. We currently depend on regional or, more commonly, hospital-specific information to monitor resistance trends. The need for incorporating the testing of older antimicrobials into antibiotic resistance surveillance systems is exemplified by the increas-

Table 1. Revived antibiotics with an indication of the current pharmacokinetic (PK) / pharmacodynamics (PD) information^a

Antibiotic	PK profiling in:		PD target derived from:	
	Volunteers	Patients	Preclinical studies	Clinical Studies ^b
Revived antibiotics				
Chloramphenicol & thiamphenicol	3	3	0	0
Colistin	1	3	2	0
Co-trimoxazole	2	1	0	0
Doxycycline	3	3	0	0
Fosfomycin IV	2	2	1	0
Fusidic acid	3	3	0	0
Methenamine	1	0	0	0
Minocycline	3	3	1	0
Nitrofurantoin	1	1	0	0
Nitroxoline	1	1	0	0
(Piv)mecillinam	2	2	0	0
Polymyxin B	0	3	2	0
Pristinamycin	1	1	0	0
Quinupristin-dalfopristin	1	0	0	0
Rifampicin	3	3	1	3
Spectinomycin	1	0	0	0
Teicoplanin	3	3	2	3
Temocillin	1	2	0	0
Trimethoprim	2	1	0	0
Examples of 'old' antibiotics in current use				
Azithromycin	3	3	2	3
Ceftazidime	3	3	3	3
Erythromycin	3	3	1	0
Flucloxacillin	3	1	0	0
Tigecycline	2	3	1	3
Tobramycin	3	3	3	3

^a(PK)/pharmacodynamic (PD) information presently available (0 = no information found; 1 = poor (≤ 3 studies/setting); 2 = fair (at least 4 studies/setting); 3 = following current standards for new drugs, including population PK analyses). ^bNote a different categorization for the PD target derived from clinical studies; only categorized as 0 (not available) or 3 (at least 1 available). Reprinted with permission from Muller AE et al. *Clin Microbiol Infect* 2015; 21:881-885.

ing resistance rates to colistin among carbapenemase-producing *Enterobacteriaceae* (CREs) that are being reported in some locations.

Thus, in the context of a global resistance threat and insufficient pipelines of new antibiotics, optimizing the use of old antibiotics—based on cutting-edge science and clinical evidence—is imperative to ensure good clinical outcome in patients and extend the life span of our older antibiotics.

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* "Risk" refers to the growing evidence of resistance of *S. aureus* and MRSA to mupirocin; "complexity" refers to the 5-day, twice-daily application protocol of mupirocin.
1. Clorox Study #9530-005 (in vitro study); 2. Clorox Study #2015-002/2015-003

APUA Headquarters in Action

APUA launches new website

APUA is delighted to announce the launch of its new and improved website! With new features and up-to-date news and media content, we're hoping you'll have an enhanced experience as you navigate through our webpages. The revamped website can be found as usual at www.apua.org. Your questions, comments and suggestions are always encouraged. Please feel free to contact us at apua@tufts.edu. Thank you for your partnership in preserving antibiotic efficacy as we strengthen society's defenses against infectious diseases.

APUA attends high-level UN meeting on antimicrobial resistance

For background information on the UN meeting, see [this APUA news article](#).

“Antimicrobial resistance poses a fundamental threat to human health, development, and security. The commitments made today must now be translated into swift, effective, lifesaving actions across the human, animal and environmental health sectors. We are running out of time,” said Dr. Margaret Chan, the Director-General of World Health Organization. Dr. Chan's [remarks](#) were delivered at an historic meeting of global leaders gathered at the United Nations General Assembly in New York on September 21, 2016—just the fourth time since its 1945 formation that the UN has convened a high-level meeting of the General Assembly formally addressing a global health crisis.

APUA Director, Jane A. Kramer, was among the scores of representatives of NGOs, antibiotic manufacturers, trade groups and academic institutes who were invited by the UN Department of Economic & Social Affairs to commit to fighting antimicrobial resistance (AMR) together. Secretary-General Ban Ki-Moon addressed the assembly, as did numerous ambassadors and health ministers of small, medium and large nations. The General Assembly issued *The United*

Nations Declaration on Antimicrobial Resistance <http://bit.ly/2d4psUR>. More importantly, a *World Health Organization Global Action Plan on Antimicrobial Resistance*, the plan for tackling AMR globally, was adopted. <http://bit.ly/2czRh77>

The occasion was dramatic and momentous, but tremendous effort must now be employed in a coordinated manner around the world.

In a preliminary meeting just prior to the UN assembly, the Center for Disease Dynamics, Economics & Policy (CDDEP), introduced hundreds of attendees to the *Conscience of Antimicrobial Accountability (CARA)*, a broad alliance of organizations from diverse interests and disciplines. The newly formed alliance is seeking partners all over the world—from industry, academia, the non-profit sector, and from student groups—inclusive of human health, animal health and environmental concerns. These are CARA's stated goals:

- Monitoring progress toward the agreed upon goals of access to effective antimicrobials for everyone across the globe;
- Identifying obstacles to progress and bringing them to light;
- Working to offer solutions to problems in all sectors; and
- Identifying, publicizing, and celebrating successes.

The early partners in CARA, including CDDEP, will be creating an organizational structure and participatory membership in the months to come. See CARA's founding document and application form here:

<http://www.forumonantibiotics.org/alliance/>

More on CARA can be viewed here:

http://www.cddep.org/blog/postsun_amr_and_cara_conscience_antimicrobial_resistance_accountability#sthash.OaHhqPga.dpuf

The UN has furnished a very informative policymakers' poster that we are pleased to share. <http://bit.ly/2d3I489>

Resistance in the News

World Bank report links antibiotic resistance to economic crisis

On Sept 19th World Bank released the report, [Drug Resistant Infections: A Threat to Our Economic Future](#). If resistance is left unchecked, it estimates healthcare costs will top \$1 trillion per year, prompting an economic crisis by the year 2050. WHO director-general Margaret Chen said, “We now know that – unless addressed swiftly and seriously and on a sustained basis – the growing global problem of antibiotic resistance will be disastrous for human and animal health, food production and global economies.” The report projected that the economic downturn would affect developing countries most profoundly, driving 28 million into poverty. According to World Bank president Jim Yong Kim, “The cost of inaction is unaffordable—especially for the poorest countries. We must urgently change course to avert this potential crisis.”

FDA bans triclosan from domestic handwash products

For some years now, the efficacy, as well as the risks, of antibacterial agents such as triclosan and triclocarban have been debated in the scientific and lay communities. In the early 2000’s, APUA president Stuart B. Levy [expressed concern](#) over the build-up of these chemicals and their potential for the development of cross-resistance to antibiotics. Following the continued buildup of environmental residues, their association with antibacterial resistance, and the possible escalation of co-resistance to antibiotics and other reported negative health impacts, the FDA has [issued a ban](#) on triclosan and [18 other antibacterial compounds](#) as additives in household hand-wash products. The FDA ban followed a one-year challenge in which manufacturers of household antiseptic washes were unable to prove the safety and superiority of long-term use of these antiseptic products. The weight of scientific evidence has demonstrated no added benefit beyond plain soap and water in preventing infection. Manufacturers now have

one year to remove these chemicals from their products. The one exception to this is antibacterial toothpaste, which was exempted because studies failed to show alterations in the mouth or gut flora of users.

Triclosan was developed in the 1960s, and continues to be employed in hospitals as a body wash for decontaminating MRSA patients and also in the food service industry. It is likewise impregnated into a large number of plastics and paints as a preservative.

UN convenes High-Level Meeting to promote sustainable antibiotic access

On September 20-21, the UN hosted a meeting urged by some of the world’s foremost experts to address the global health threat posed by antibiotic resistance. With global deaths attributed to resistance estimated at 700,000, many more deaths are caused by insufficient access to antibiotics. For the first time, a *One Health* issue was discussed at this high level. The call for the meeting, issued by Ramanan Laxminaryan and colleagues in the [Lancet](#) requested a coordinating mechanism with four functions: 1) a global campaign to raise awareness; 2) monitoring of defined targets to reduce global deaths from lack of access; 3) mobilization of financial resources from donors, aid agencies and countries; and 4) coordinated action across multiple sectors including animal husbandry, humans and the environment.

The meeting was preceded by an article authored by top-level scientists in the journal [Science](#) who proposed that \$5 billion are needed annually to combat the antibiotic resistance problem. The funding would support a coordinated worldwide response that includes global systems for monitoring resistance.

For more updated outcomes of this meeting, see [APUA attends high-level UN meeting on antimicrobial resistance](#).

New guidelines proposed for wound care

Treatment of wounds is one of the most common reasons for antibiotic use in hospitals. As reported in *The Journal of Antimicrobial Chemotherapy*, an international group of experts has stepped in to provide for the first time, much needed guidelines on the proper use of antimicrobials in the care of skin and soft tissue infections. The [position paper](#), produced by the British Society for Antimicrobial Chemotherapy and the European Wound Management Association offers to set some standards in an area of antibiotic overuse. Besides patient expectations for antibiotic prescriptions, antibiotics have been overused in instances of simple inflammation without infection, and for unnecessarily long periods i.e., until the completion of healing. The four elements set forth for antimicrobial stewardship in wound care are:

- ◆ Only wounds exhibiting classic signs of inflammation should be considered infected.
- ◆ Empiric treatment with antibiotics should be based on infection severity and the available clinical and microbiological data.
- ◆ Any clinically infected wound should be cultured for pathogen determination and susceptibility profiling.
- ◆ Antibiotic therapy should be restricted to the shortest possible duration.

Where possible, the authors also recommend guidance by a dedicated antimicrobial stewardship team working alongside a wound care team.

Go [here](#) to see the abbreviated algorithm for antibiotic treatment of wounds.

Large food corporations yield to pressure for antibiotic reduction

Following an earlier move in March to reduce antibiotics in cattle production, the giant U.S. meat processor, Cargill, has [ceased the routine use](#) of gentamicin in the production of its two largest turkey brands—affecting 50 million birds. This is significant because gentamicin is an important drug in the treatment of human infections.

In similar fashion, Perdue Farms has [eliminated routine antibiotics](#) from over half of its turkeys and both Perdue and

Tyson foods have ceased gentamicin use in their chicken rearing.

In early August, MacDonald's [announced the removal](#) of human-use antibiotics from its chicken supply, well ahead of schedule. The companies continue to use these antibiotics for treating sick animals and halting further spread of disease.

CARB-X to spur antibiotic development

A new international partnership, dubbed [CARB-X](#), for “Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator” has pledged \$350 million dollars to accelerate development of promising antibiotic drugs, diagnostics and vaccines over the next 25 years. Considered to be a “watershed moment” by BARDA’s acting director, Richard Hatchett, the large international public-private partnership represents the unification of governments, academics, industry and NGO’s to address the major public health threats posed by antibiotic resistance. The funds, pledged by multiple U.S. (BARDA, NIAID, the Broad Institute) and British-based institutions (Wellcome Trust, AMR Centre), will be used to propel promising antibiotic candidates through the notoriously risky early stages of preclinical development in which many promising candidates tend to fail for multiple reasons. MassBio and RTI international will provide business and technical/regulatory support, respectively.

CARB-X, which emerged from President Obama’s 2015 CARB initiative, is headquartered at the [Boston University School of Law](#) and led by Professor Kevin Outterson, who was [APUA’s 2015 recipient](#) of the *APUA Leadership Award*. According to Outterson, “The bulk of the money will go to research labs and small companies developing innovative products all over the world...We’re trying to build a fire station before the buildings catch on fire.”

See Dr. Outterson’s latest publication: *Delinking Investment in Antibiotic Research and Development from Sales Revenues: the [Challenges of Transforming a Promising Idea into Reality](#)*.

Upcoming Events

October 3-5, 2016:

2nd World Congress and Exhibition on Antibiotics ([Antibiotics 2016](#)). London, UK

October 26-30, 2016:

[IDWeek 2016](#), New Orleans, Louisiana

October 29 - November 2, 2016:

[American Public Health Association Annual Meeting and Expo](#). Denver, Colorado

November 14-20, 2016:

[CDC's Get Smart About Antibiotics Week](#).

November 30 - December 3, 2016:

[16th Asia-Pacific Congress of Clinical Microbiology and Infection](#) (APCCMI) Melbourne, Australia

February 23-25, 2017:

Australian Society for Antimicrobials 18th Annual Scientific Meeting ([Antimicrobials 2017](#)). Adelaide, Australia

February 26 - March 3, 2017:

[Antimicrobial Peptides Gordon Research Conference](#).
Ventura, California

February 27, 2017:

[7th Clinical Microbiology Conference](#). Amsterdam, The Netherlands

April 22-23, 2017:

[Global Health and Innovation Conference](#).
Yale University, New Haven, Connecticut

April 22-25, 2017:

27th European Congress of Clinical Microbiology and Infectious Diseases ([ECCMID](#)). Vienna, Austria

June 1-5, 2017:

[ASM Microbe 2017](#). New Orleans, LA, USA

June 14-16, 2017:

[Association for Professionals in Infection Control and Epidemiology \(APIC\) Annual Conference](#).
Portland, Oregon, USA

Minnesota adopts *One Health* approach to antibiotic stewardship

In July, the state of Minnesota launched a multi-department, multi-faceted [5-year plan](#) that incorporates both human and animal health experts to promote better understanding of *One Health* antibiotic stewardship and to control the rise in antibiotic resistance. The plan hopes to coordinate the efforts of 4 agencies to reduce tensions between animal and human sectors and utilize a model that will develop an antibiotic “footprint” tool to assess antibiotic persistence in the environment.

South African hospitals implement antimicrobial stewardship with promising results

Authors Adrian Brink and colleagues have [reported](#) the results of antimicrobial stewardship implementation in 47 South African hospitals. The study utilized an audit and feedback strategy conducted by pharmacists in settings with limited infectious disease resources. Following a baseline survey of stewardship activities, audits were implemented to reduce antibiotic consumption resulting from prolonged duration, as well as redundant, multiple antibiotic coverage. The study of over 116,000 patients conducted between 2009 and 2014 showed that nearly 1 in 15 prescriptions required intervention—39% of which were for excessive duration. The intervention led to an ~18% reduction in antibiotic use (from 101 to 83 DDD/100 patient days), demonstrating that basic interventions could result in significant returns despite limited infectious disease resources.

Hygiene updates: hospital floors, shoes and doctors' hands targeted in pathogen spread

In a recent [study](#) in *Infection Control and Hospital Epidemiology*, Sreelatha Koganti and colleagues describe using the non-pathogenic bacteriophage MS2 as a surrogate for tracking the potential spread of nosocomial pathogens from a hospital isolation room floor. Following inoculation, the phage was found on 40% of patients' hands by day 1, on 63% by day 2, and on 43% by day 3. It appeared on high-touch

Publications of Interest

surfaces in adjacent rooms, the nursing station, and on portable equipment including wheel chairs, med carts, vital signs equipment and pulse oximeters. The authors concluded that floors may be under-appreciated as a reservoir of pathogen transmission, and noted that shoes, socks and slippers are often touched by hands. Furthermore, it's not uncommon for call buttons and blood pressure cuffs to fall on the floor.

Corroborating this evidence is a new [systematic review](#) of 13 studies that examined the role of shoes as a vector for pathogen transmission. Reported by RT Rashid et al, in the Journal of Applied Microbiology, the review found a high frequency of the pathogens MRSA, *Clostridium difficile* and MDR gram-negative species, among others, on shoe bottoms in healthcare as well as other settings.

Another confirmed pathway of pathogen transmission in the hospital is via the hands of healthcare workers. Breaking this chain with adequate hand hygiene has long been a priority, but influencing human behavior to act accordingly has proved challenging. A recent [surveillance study](#) conducted at the Santa Clara Valley Medical Center in San Jose, CA showed a marked difference in hand hygiene compliance when comparing the records of two different groups of hygiene auditors. While infection prevention nurses recorded compliance rates of 57%, hospital volunteers (who were unrecognized in their surveillance role), recorded rates of only 22%. The difference was attributed to the “Hawthorne Effect”—a change in behavior when one is being observed.

The stark contrast highlighted the need for more aggressive interventions, such as implementing CDC's [Clean Hands Count Campaign](#), which empowers patients to hold healthcare workers accountable for cleaning their hands. Other methods being examined and tried are: 1) monitoring devices which keep track of alcohol dispenser usage; and 2) publicizing hospital compliance data, which can create healthy inter-department competition.

Domestic pets pose risk of superbug transmission

It has been known for some time that domestic pets can harbor MRSA, and more recently, shown that humans and pets can

- [Delinking Investment in Antibiotic Research and Development from Sales Revenues: The Challenges of Transforming a Promising Idea into Reality](#) K Outterson et al. *PLoS Med* (Jun 2016)
- [Time to Abandon the Hygiene Hypothesis: New Perspectives on Allergic Disease, the Human Microbiome, Infectious Disease Prevention and the Role of Targeted Hygiene](#) SF Bloomfield et al. *Perspect Public Health* (July 2016)
- [One Health and the Politics of Antimicrobial Resistance](#) LH Kahn. *Johns Hopkins University Press* (Jun 2016)
- [‘The Rise of India’s Superbugs:’ A Look at Why Thousands of Babies are Dying in India](#). *Malay Mail Online* (Aug ‘16)
- [CIDRAP Antimicrobial Stewardship Podcast](#) (ASP) D Nathwani. (Aug 2016)
- [Executive Summary: Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society](#) AC Kalil et al. *Clin Infect Dis* (Sept 2016)
- [Probiotics Could Offer Important Line of Defense Against Drug-resistant Bacteria](#) EV Keet. *Contagion Live* (Aug 2016)
- [Vaccines for Healthcare-associated Infections: Promise and Challenge](#) JM Knisely et al. *Clin Infect Dis* (May 2016)
- [Tackling Antimicrobial Resistance in Developing Countries: The Role of Aid and International Agencies](#) J O’Neill et al. Center for Global Development (Jun 2016)
- [Online Antimicrobial Stewardship Course](#). Collaboration between University of Dundee and the British Society for Antimicrobial Chemotherapy (Begins Sept 19, 2016)
- [An Updated View of Plasmid Conjugation and Mobilization in Staphylococcus](#) JP Ramsay et al. *Mob Genet Elements* (Jul 2016)
- Webinar: One Health and the Politics of Antibiotic Resistance ([Part 1 of 2](#)). Find the book [here](#).
- [Drug Repurposing: A New Front in the War Against Staphylococcus aureus](#) S Das et al. *Future Microbiol* (Aug 2016)

share isolates of the same bacterial strain. Still, the risk of bacterial exchange is considered low, and more likely to occur in the direction of humans to animals than the reverse. Now, a new [study](#) by Chinese researchers has reported finding a pet shop worker, four dogs and two cats in close contact that were infected with *E. coli* carrying MCR-1—a gene that encodes resistance to the last-resort antibiotic, colistin. The study expands the reservoirs of concern to include domestic pets, and adds to the worries of veterinarians that drug resistance in pets may be escalating. Of greater concern are increasingly resistant strains of *E. coli* and *Salmonella* that colonize and shed from pets and potentially cause severe illness in humans.

Jeff Bender, DVM and member of the American Veterinary Medical Association's Task Force for Antimicrobial Stewardship in Companion Animals, admits that the rate of antibiotic use in pets is entirely unknown—but suggests that it may approximate that in human medicine—50%. He and others agree on the need for national surveillance of pets.

10% of patients import superbugs into hospitals

In a [new study](#) of over 5,000 patients entering 6 German hospitals, researchers were surprised to find that 9.5% (nearly one in 10 patients), is carrying a multidrug resistant pathogen—most commonly an *E. coli* bearing resistance to a third-generation cephalosporin. Beta-lactamases of the CTX-M-1 and CTX-M-9 were the most common types found, and five patients carried carbapenemase-producing *Enterobacteriaceae*. Patients who had travelled outside of Europe and those who had consumed antibiotics previously were the most likely carriers of the latter pathogen type.

U.S. survey reveals excessive non-prescription antibiotic abuse

A Houston, Texas [survey](#) of 400 demographically diverse adults has revealed some unanticipated patterns regarding household antimicrobial usage. While just 5% of responders had used non-prescribed antibiotics in the previous year, 14% reported storing antibiotics for future emergencies, and 25%

intended to use them at some point. The drugs were consumed mostly for colds, for which antibiotics are contraindicated. Researchers were also surprised by some of the sources: while 12% stashed leftover drugs from previous prescriptions, 20% obtained them from friends and family; 40% claimed the ability to purchase antibiotics without a prescription in U.S. pharmacies; and 24% purchased outside the country. Another 4% voluntarily shared that they used [antibiotics intended for their pets](#)—a practice deemed risky, as these drugs are formulated for animal metabolism, which differs from that of humans. The findings underscore the need for renewed efforts to educate the public and counteract detrimental habits that continue to exacerbate the antibiotic resistance problem.

China resolves to confront antimicrobial resistance

In China, where antibiotics are widely available without prescription, it is predicted that premature deaths from antibiotic resistant illness will cost the country \$20 trillion by 2050. In late August, the Chinese central government mobilized 14 of its ministries and departments in a [multi-point National Action Plan](#) to address antimicrobial resistance. By 2020, the comprehensive plan aims to: develop new antimicrobials; implement prescription-only antimicrobial sales; intensify surveillance of human and veterinary usage, and amplify training and education for healthcare workers and consumers.

China accounts for half the world's antimicrobial consumption. In addition to ease of access and high demand, China is hampered by a lack of rapid diagnostics, leading to an over-reliance on antibiotics where they are not needed.

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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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