

## **NEWSLETTER**

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### Assessing MDR Pathogens in Humans, Pets and the Environment

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## Prevention and Control of Methicillin-Resistant *Staphylococcus aureus* (MRSA): Biology, Research, and Intervention

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We live at a time of infectious disease threats from increasingly resistant bacteria that encompass what are referred to as multidrug-resistant (MDR) pathogens. These organisms have arisen in many parts of the world and then spread globally. When they cause clinical infection, the result is difficult-to-treat disease, leading to increased mortality and healthcare cost. The World Health Organization states that people infected with methicillin-resistant Staphylococcus aureus (MRSA) are 64% more likely to die than those whose disease is due to a sensitive variety of S. aureus. 1 If no action is taken, a conservative estimate is that by 2050 there will be 10 million annual deaths from antimicrobial resistant infections worldwide; this will be the leading cause of mortality with an economic cost exceeding \$100 trillion each year.<sup>2</sup> Thus, it is imperative that we understand the biology relating to emerging resistance and spread of these organisms so that effective control strategies can be developed and deployed. Peterson and Schora recently reviewed the large studies performed whose main goal was to reduce MRSA infection.<sup>3</sup> From their analysis it appears that active surveillance testing (e.g., screening) is invariably linked to a successful program if the goal is very low rates of MRSA clinical disease and they proposed threshold targets for determining a successful program (Table 1).3 In this review all the successful programs used real-time PCR (qPCR) as the

laboratory screening test. However, much debate remains over the 'best' approach for control of MDR pathogens, with hand hygiene consistently stressed as the best core measure to effectively control all healthcare associated infections (HAIs).<sup>4</sup> However, when the impact of enhanced hand hygiene was prospectively studied in a multicenter trial, there was no impact on MRSA clinical disease.<sup>5</sup> For the understanding of MDR pathogen control, it is prudent to understand the biology of antimicrobial resistance development and spread in key pathogenic bacteria so as to devise solutions likely to be effective in preventing such events. The purpose of this commentary is to i) briefly describe biologic traits of MDR pathogens that influence what control measures are likely to be effective, ii) discuss key literature issues that contribute to controversy regarding best infection control practices for MRSA, and iii) present the argument that setting clinical disease threshold goals may be preferable to mandating process measures for solutions for MDR infection prevention.

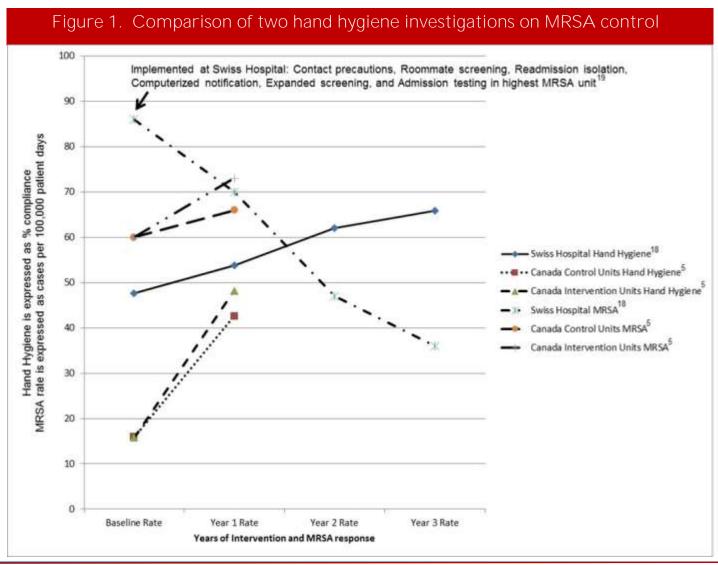
Antimicrobial resistance generally depends on two key elements, the first being loss of susceptibility to a therapeutic agent, occasionally during treatment, by either selection of resistant strains or the mutation/acquisition of genes coding for new resistance trait(s). This is followed by the second element of subsequent dissemination of the adapted organisms to additional persons locally, regionally, and globally.<sup>6</sup> While

Table 1. Recommended thresholds that if not met should trigger more intensive efforts for MRSA control.<sup>3</sup>

	Clinical Cultures	Blood Cultures		
Target Rate	<0.3/1,000 patient days	<0.03/1,000 patient days		

intervening in this MDR problem seems straightforward, it is critical to understand how these elements (MDR development and dissemination) interact in order to optimize the design of control strategies. In general, Gram-negative bacteria tend to have high genome plasticity and are capable of frequent new resistance acquisition (e.g., panmictic evolution) - they are currently considered a great MDR threat.<sup>7-8</sup> For this setting, antimicrobial stewardship can be critical in preventing the development of new resistance while infection control barrier precautions may be less important (e.g., to prevent spread) unless a particularly virulent clone(s) arises. Conversely, Gram-positive MDR bacteria tend to be highly clonal, 10-13 with less ongoing emergence of new resistant strains, and are typically effectively managed using infection control surveillance with contact precautions (e.g., isolation) for those found harboring

these strains.<sup>14</sup> MRSA is a good example of this MDR problem where spread of resistant strains is common (clonal evolution), with only 10 clonal complexes, or lineages, of S. aureus dominating in human disease and eight of these acquiring the mobile genetic element (e.g., staphylococcal cassette chromosome (SCC) that carries either mecA or mecC (SCC*mec*)) coding for methicillin resistance. <sup>12-13. 15</sup> Preventing infections from MDR bacteria with a clonal biology background seems best approached by preventing horizontal dissemination through use of infection control isolation often called 'barrier precautions'. 3, 14 A third avenue for outbreaks of nosocomial MDR bacterial infection is by dissemination from an environmental reservoir, or point source within the hospital setting. These events are less common, but when they occur require a diligent search for the source of the MDR pathogen followed by its elimination. 16 The point of this



discussion being that it should be expected that varying infection control practices will be needed in order to contain and prevent the differing types of healthcare-associated infections encountered within the acute care setting. Thus, it is unlikely that a single 'one size fits all' approach will be successful for comprehensively preventing HAIs when planning the best practice(s) to improve patient safety.

A reasonable question is, "Why is there no consensus on how to reduce MRSA infection and what is the reason(s) for the divergent literature?" An interesting commentary was recently published by Kavanagh and colleagues. They make the case that when one reads the Infectious Diseases literature it is important to carefully examine the entire report as the data is not always fully represented by the abstract and

discussion sections. While one could argue with the authors' assessment, it is helpful to consider their argument when the issue of MRSA control is discussed. For example, perhaps the critical report most cited to make the case for hand

"...it is unlikely a single 'one size fits all' approach will be successful for comprehensively preventing HAIs when planning the best practice(s) to improve patient safety."

hygiene as the mainstay in MRSA control is that from Pittet et al. 18 This investigation concluded that "the (hand hygiene) campaign produced a sustained improvement in compliance with hand hygiene, coinciding with a reduction of nosocomial infections and MRSA transmission", but, as is the case with many Infection Control studies, more than one intervention was occurring at the same time. In this case, at the introduction of the hand hygiene intervention campaign, the hospital center also implemented contact precautions for MRSA positive patients, roommate screening for patients found to be positive, readmission isolation for known MRSA positive patients, computerized notification of nursing units as to patient MRSA status, expanded screening for MRSA carriers, and admission active surveillance testing in the highest MRSA unit. 19 The report describing this separate but simultaneous intervention concluded that 'infection control measures had a substantial impact on both the reservoir of

MRSA patients and the attack rate of MRSA bacteraemia.<sup>19</sup> Separating the impact of enhanced hand hygiene from these other infection control measures is challenging at best.

Another investigation was a prospective, cluster-randomized trial on the impact of improved hand hygiene on MRSA infection.<sup>5</sup> They found that even with a statistically significant improvement in hand hygiene, MRSA colonization was not reduced. A comparison of the results of these trials is in Figure 1, which demonstrates the complexity of interpreting published literature as well as the conflicting results.

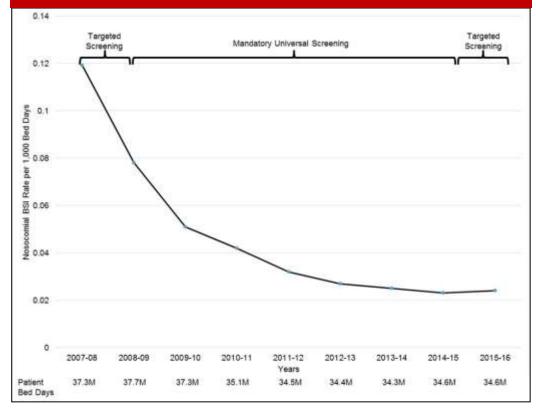
A final report in this context is that from Grayson and colleagues who found that improving hand hygiene from 21% compliance to 48%/47% after 12 and 24 months, respectively, reduced MRSA clinical isolates from 139

positives per 10,000 patient discharges to 73, and reduced MRSA bacteremia from 5 cases per 10,000 discharges to 2 ( $P \le .035$  for MRSA trends).20 This report suggests hand hygiene improvement can modestly impact MRSA disease, particularly if clinical infection rates are high -

but the final disease rate remained above the thresholds recommended in Table 1. A recent critical review of the topic concluded that "interventions to improve hand hygiene may reduce the incidence of HAIs and improve hand hygiene rates, but the quality of evidence is low".<sup>21</sup> All this suggests that hand hygiene alone cannot control MRSA.

As noted earlier, our recent review of large studies that focused on MRSA control concluded that active surveillance testing was part of all successful programs achieving a very low MRSA infection rate. We suggested that a key change in concept for policy makers, healthcare societies, and public health organizations would be to set threshold targets for levels of MRSA disease that were achievable, rather than mandating specific infection control processes – thus encouraging both historic and novel practices that can include expanded isolation, qPCR, and new technology.<sup>3</sup> The MRSA

Figure 2. MRSA hospital-acquired blood stream infection rates in British healthcare



clinical disease threshold targets we suggested were very low, but are based on disease rates from large published studies (Table 1).<sup>3</sup> One data set not included was from the English National Healthcare System that undertook a country-wide program to reduce MRSA bloodstream infection (MRSA BSI).<sup>22</sup> Over 9 years, which included nearly 320 million patient days, they achieved a large (>4-fold) reduction in MRSA BSI (Figure 2). In this program, while active surveillance testing was primarily performed using chromogenic agar culture;<sup>23</sup> their outcome suggests that a comprehensive, all inclusive, national program using active surveillance testing can detect the majority of MRSA colonized patients needing contact precaution isolation whenever in the hospital. This program was associated with a significant and meaningful reduction in MRSA blood stream infections that met the threshold suggested in Table 1. These results indicate a large national program achieving a very low rate of MRSA clinical disease remains achievable.

The United States has experienced a tortuous evolution in dealing with the significant threat of MRSA.<sup>24</sup> It is time for

policy makers to take a new approach to elimination this disease threat. **MRSA** infection remains one of the most cost-effective diseases to prevent, where the cost of treating MRSA clinical infection far exceeds the prevention.<sup>3,25-27</sup> expense of challenge will Solving this provide benefits of enhanced patient safety, healthcare quality, and reduced cost. Setting of clinical acceptable **MRSA** disease thresholds can be the 'winning' approach to challenge in a society that embraces options and choices. Either penalizing hospitals for not achieving MRSA clinical disease goals, or rewarding those that do - or a combination of

both – is a strategy that can facilitate reduction in MRSA disease and inspire innovation. Now is the time for U.S. policy makers to take patient safety seriously and embrace MRSA infection as a problem that can be solved.

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### Multidrug-Resistant Bacteria in

### Man's Best Friends

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Pets—with dogs and cats being the most popular—have long been considered members of the family, living under the same roof and sharing the same cozy environment. They also take advantage of the latest medical technologies currently implemented in veterinary medicine. Infectious diseases are treated with the latest generation of antibiotics including critically important cephalosporins and fluoroquinolones, and in some cases with last-line antibiotics from human medicine.

The use of many different classes of antibiotics in animals has contributed to the selection of antibiotic-resistant microcosm within the normal flora of animals, and the establishment of healthcare-associated multidrug-resistant bacteria in veterinary settings. Some bacteria found in dogs and cats have become virtually resistant to all antibiotics used in veterinary medicine. Some have a zoonotic potential and behave as opportunistic pathogens causing different types of infections, while others only colonize healthy carriers, posing the risk that they silently spread their multi-drug bacteria in the household and further into the community.

#### Methicillin-resistant staphylococci

S. pseudintermedius is a typical example of a bacterium from the normal flora of a dog, which has become resistant to almost all classes of antibiotics. Methicillin-resistant S. pseudintermedius (MRSP) emerged a decade ago and represents one of the most challenging bacteria in veterinary medicine. Some of the strains are only susceptible to antibiotics used as a last resort for the treatment of staphylococcal infections in humans e.g. linezolid and vancomycin (Table 1). Specific epidemic clones have been spreading worldwide with clonal complex CC71 being the most predominant, CC68 originated mostly through

North America and is now increasingly found in Europe, CC258 is localized in Europe and CC45 in Asia<sup>1</sup>. Dogs can be happy, healthy carriers of MRSP until they develop severe infections associated with skin diseases, or after a wound or surgery. The types of infections are multiple including pyoderma, otitis and sinusitis as well as post-surgical wound and bone infections.<sup>2</sup> Antimicrobial therapeutic options are very limited.

The close proximity of dogs and owners constitutes the ideal melting pot for the exchange of bacteria. Between four and thirteen percent of owners of pets with MRSP infections were also found to be nasal carriers of the bacteria, increasing the risk of developing an MRSP infection. A first case of post-operative sinusitis in humans caused by MRSP and associated with dogs was reported in the U.S. in 2009 as "Beware of the pet dog: a case of *Staphylococcus intermedius* infection". Cultures and bacterial fingerprinting analysis confirmed that the isolate from the patient's pet dog was identical to that of the patient. The patient could only be successfully treated with a prolonged antibiotic therapy with vancomycin and linezolid.

One year later, a similar case of sinusitis was reported in Switzerland where the patient was infected with the same MRSP clone of sequence type ST71 that has been spreading in dogs throughout Europe.<sup>5</sup> Since then, several additional cases of human infections, almost all related to dog exposure, have confirmed the zoonotic potential of *S. pseudintermedius*.<sup>6</sup> Although less frequent than MRSP, methicillin-resistant *S. epidermidis*, *S. haemolyticus*, and *S. aureus* belonging to similar clonal lineages as those found in humans can also colonize and cause severe infections in companion animals also emphasizing transmission between humans and animals.<sup>7-10</sup> Similarly

Table 1. Examples of multidrug resistance profiles in predominant lineages of bacteria from dogs and cats

Destado	C				
Bacteria	Sequence type	Classes of antibiotics with resistance			
Staphylococcus pseudintermedius	ST71, ST68, ST45, ST238	Beta-lactams, trimethoprim, sulfonamides, fluoroquinolones, tetracyclines, macrolides, lincosamides, aminoglycosides, chloramphenicol			
Staphylococcus au-	ST22	Beta-lactams, trimethoprim, fluoroquinolones			
reus	ST1	Beta-lactams, trimethoprim, tetracyclines, macrolides, lincosamides, am noglycosides, streptomycin			
	ST5	Beta-lactams, macrolides, lincosamides, aminoglycosides, chloramphenicol, fluoroquinolones, mupirocin			
Staphylococcus epi- dermidis	ST2	Beta-lactams, aminoglycosides, macrolides, lincosamides, tetracyclines, trimethoprim, sulfonamides, fluoroquinolones			
Staphylococcus hae- molyticus	ST1	Beta-lactams, aminoglycosides, macrolides, lincosamides, tetracyclines, trimethoprim, sulfonamides, fluoroquinolones, chloramphenicol			
Acinetobacter bau- manii	ST1, ST2, ST10	Beta-lactams/beta-lactamase-inhibitors, 2 <sup>nd</sup> and 3 <sup>rd</sup> generation cephalospoins, aminoglycosides, fluoroquinolones, trimethoprim, sulfonamides, tetra cyclines and tigecycline			
Klebsiella pneu- moniae	ST11, ST15, ST101	Beta-lactams including 3 <sup>rd</sup> generation cephalosporins, aminoglycosides, trimethoprim, sulfonamides, tetracyclines, fluoroquinolones, (carbapenem)			
	ST274	Beta-lactams including 3 <sup>rd</sup> generation cephalosporins, aminoglycosides, trimethoprim, sulfonamides, tetracyclines, quinolones			

to MRSP, they are also frequently resistant to several classes of antibiotics (Table 1).

Multidrug-resistant Klebsiella pneumoniae and Acinetobacter baumannii

Klebsiella pneumoniae and Acinetobacter baumannii are a major cause of severe healthcare-associated infections in human hospitals. Levels of antimicrobial resistance have been increasing throughout the past decade with some strains exhibiting resistance to all classes of antibiotics. They are also circulating in veterinary clinics and companion animals are not excluded from becoming infected with such multi-drug resistant bacteria. Dogs and cats may already be carriers of multidrug-resistant K. pneumoniae and A. baumannii or, like humans, they can contract them during hospitalization in a veterinary clinic which may act as a turntable for the spread of these multidrug-resistant life-threatening bacteria. Some multidrug-resistant K. pneumoniae and A. baumannii clones from

companion animals are similar to those found in humans and have also established themselves in the veterinary settings. Many have been found to be resistant to several antibiotics including critically important cephalosporins and fluoroquinolones with the exception of carbapenems, a class of antibiotics used as an absolute last resort in human medicine and not licensed for veterinary use (Table1). Despite this restriction, carbapemems are in some cases being used off-label for the treatment of urinary tract or post-operative infections in companion animals caused by multidrug-resistant Enterobacteriacae, posing the risk of selecting carbapenem-resistant strains.11 Such off-label veterinary use should be strongly discouraged, since acquired carbapenem resistance has already been reported among strains from dogs and cats mainly associated with plasmid and transposon-mediated  $bla_{OXA-48}$  in K. pneumoniae and bla<sub>OXA-23</sub> in A. baumannii. 12,13 Uncontrolled use of carbapenems in companion animals may rapidly contribute to an increase of existing carbapenem-resistant bacterial populations in animals. This could jeopardize one of the most critical antibiotics for human medicine since animal-to-human-transmission was demonstrated, placing pet owners at risk of also becoming colonized with life-threatening multi-drug-resistant bacteria.

#### It is time to be cautious

Emergence of multidrug-resistant bacteria in animals has limited therapeutic options, leading to an increased risk that antibiotics used as a last resort in human medicine are also used in companion animals. In the absence of any other alternatives, these antibiotics can also be legally applied in the treatment of companion animals. However, use of these antibiotics should be strongly avoided and be kept only for the treatment of lifethreatening bacterial infections in humans. For instance, selection of resistance to last-line antibiotics in S. aureus, A. baumannii, and K. pneumoniae may have dramatic consequences as these bacteria represent one of the most serious burdens to hospitals with often fatal consequences. In veterinary settings, it is also necessary to establish and maintain continuous and strict infection control strategies following guidelines for prudent use of antimicrobials, such as those recently released by the European Union.<sup>14</sup> We should all be aware that multidrugresistant bacteria with zoonotic potential are spreading among cats and dogs. They may become a concern for every household and may represent a risk for both animal and human health. It is imperative to avoid close proximity and contact with animals under antimicrobial therapy or that have been recently hospitalized in a veterinary clinic, and strict hand hygiene remains one of the most important measures in preventing transmission. Nevertheless, the presence of multidrugresistant bacteria in pets emphasizes that the cautious, prudent and prioritized use of antibiotics belongs to the global onehealth concept in order to maintain effectiveness of all existing antimicrobials for all members of a family.

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### Environmental Spread of Multidrug-Resistant Pathogens in a Hospital Laundry Facility

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"Laundry facilities that process hospital

and clinic linens should be considered an

extension of the healthcare environment,

even when the facility is not physically

located on site."



Michael

In an effort to evaluate the threat of antibiotic resistant bacteria in the U.S., the Centers for Disease Control (CDC) developed three classifications of pathogens; "urgent", "serious" and "concerning", based on the severity of the disease, cost of treatment and difficulty of treatment. 1 Clostridium difficile has been classified as an "immediate public health threat that requires urgent and aggressive action", even though it does not have clinically relevant antibiotic resistance at this time.

Methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus faecalis and E. faecium (VRE) were classified as "serious" threats which "require prompt and sustained action to ensure that the problems do not grow". All three pathogens

have the ability to survive on fomites for extended periods of time and are difficult to remove from the environment by standard cleaning and disinfection protocols, increasing the chance that the next patient to occupy the room will be colonized. Personnel protective equipment is required when entering a patient's room with any of these three pathogens. However, no special precautions are taken with the soiled laundry once the patient has left and the room is cleaned. These contaminated linens are placed into dirty laundry bags with other soiled linens from the same ward and sent off to the laundry facility without any identification stating that they may

Laundry facilities that process hospital and clinic linens should

be contaminated with high precaution pathogens.

be considered an extension of the healthcare environment, even when the facility is not physically located on site.<sup>2-5</sup> It is estimated that 5 billion pounds of health care-associated fabrics are laundered in the U.S. annually, and heavily contaminated textiles can contain up to 10<sup>6</sup> to 10<sup>8</sup> cfu per 100 cm<sup>2.6</sup> Limited studies have assessed the potential risk to exposed laundry workers who handle dirty hospital linens. A very few cases have documented illness (12 cases of hepatitis and eight cases of Salmonella poisoning) related to exposures to soiled linens.<sup>4</sup>

> Other reports of infections potentially Norovirus.<sup>7</sup>

among laundry workers include Staphylococcus aureus infections and viral gastroenteritis-In Taiwan, a laundry worker was suspected to be the index case in a SARS viral epidemic within

the community.8 Laundry workers are also at physical risk of cuts and abrasions due to sharps and medical devices left in and among the linens. These medical devices may also be contaminated with infectious body fluids which can cause blood infections.

We undertook a study of "soiled" and "clean area" surfaces in order to determine the level of contamination of C. difficile, MRSA, and VRE within the environment of a commercial laundry facility that services six Seattle area hospitals and 30 outpatient clinics. 9-11 Approximately 300,000 pounds of laundry are processed each week. Over 98% of the linens cleaned are owned by the laundry and processed in one line where they are sent down chutes to the 1<sup>st</sup> floor for cleaning. A 2<sup>nd</sup> processing line is used for customer-owned goods [COG] (2%). These are sorted in a separate area of the facility, manually placed into washers on the 1<sup>st</sup> floor and washed in smaller batches. All clean laundry is dried, sorted, folded and packaged for delivery on the first floor "clean areas.

To build on the limited knowledge base available for these critical pathogens in the laundry processing environment, we collected and evaluated 240 surface samples from both "dirty" and "clean area" sites at four time points in 2015—thirty-five samples at each time point from a single surface; and 25 samples from 2 or more surfaces. Three parallel enrichment processes were utilized to independently target one of the three pathogens (*C. difficile*, MRSA and VRE) from each surface sample.

Of the 120 samples collected from the dirty areas, 21% (n=25) were positive for C. difficile, 28% (n=33) were positive for MRSA and 53% (n=64) were positive for VRE. On the clean side 2% (n=2) were positive for C. difficile, 3% (n=3) were positive for MRSA and 8% (n=10) were positive for VRE. The dirty area had statistically higher contamination rates than the clean area for contamination with  $\geq$ 1 pathogen (65% dirty

area vs 9% clean area, p<0.001). Dirty vs. clean areas rates were as follows: *C. difficile* (21% vs 2%, p<0.001), MRSA (28% vs. 3%, p<0.001) and VRE (53% vs. 8%, p<0.001).

The primary and secondary sort dirty areas showed the highest prevalence of positive samples for all pathogens, both overall and for individual pathogen. Overall, contamination was highest at 87.5% in both the primary and secondary sort, 62.5% in the COG area, 45.8% in the COG washers, 28.3% in the receiving area, 9.2% in the break area and 0% in the folding and processing areas (Fig 1). There were significant correlations among pathogens. Ten out of 240 (4.2%) samples contained all three pathogens. Seventeen (7.1%) samples contained both MRSA and VRE. The strongest correlations were between MRSA and VRE (0.6357, p<0.0001), followed by C. difficile and VRE (0.6120, p<0.0001), with a moderate correlation between *C. difficile* and MRSA (0.4880, p<0.0005). The odds of observing contamination with one or more pathogens in the dirty area was 18.0 times higher than in the clean areas (Table1).

Seasonal variation was observed in the dirty area for *C. difficile*. *C. difficile* toxins A and/or B were present in 64%

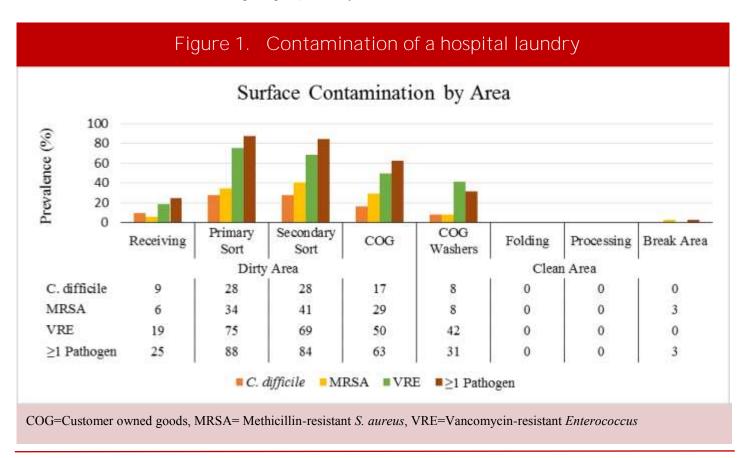


Table 1. Probability (Odds Ratio) of Contamination in Dirty Area Compared to Clean Area

Location	Any Pa	thogen	C. diffi	cile	MRSA	4	VRE	
	OR	CI	OR	CI	OR	CI	OR	CI
Clean Area	1		1		1		1	
All Dirty Areas	18.0*	8.9-36.5	15.5*	3.6-67.2	14.8*	4.4-49.8	12.6*	6.0-26.3
Receiving	3.3**	1.2-9.1	6.1	1.0-38.2	2.6	0.4-16.3	2.5	0.8-7.6
Primary Sort	69.4*	20.5-234.3	23.1*	4.7-113.9	20.4*	5.3-79.5	33.0*	11.8-92.4
Secondary Sort	53.0*	17.1-166.9	23.1*	4.7-113.9	26.7*	6.9-102.5	24.2*	9.0-65.1
COG	16.5*	5.9-46.4	11.8**	2.0-68.7	16.1*	3.8-68.1	11.0*	3.9-30.8

\* p<0.001, \*\* p<0.05

of all isolates from the dirty area. Of these, 10 isolates carried both genes.

Contamination in the dirty area was highest in April with a prevalence of 40% (n=12) and was statistically higher than both January (10%, p=0.012) and July (13%, p=0.025), but not October (20%, p>0.05). MRSA contamination was highest in July (40%, n=12) and VRE had the highest levels of contamination in April (57%, n=17), but no statistical difference by sample date was observed for either pathogen (p>0.05). In the clean areas, the number of positive samples were very low and showed very little seasonal difference in prevalence.

Inherent limitations, such as the difficulty in culturing specific bacteria (i.e., C. difficile spores), and differences in incubation times and media used, may have led to an underestimation of the true prevalence for each of the pathogens. 9-11 Additional studies will be needed to demonstrate if there is a clear risk to facility workers. Future studies comparing the whole genomes of both the human and environmental isolates would help to elucidate the relationship between the strains from the contaminated laundry environment and those isolated from laundry personnel. In addition, whole genome analysis would allow one to determine if isolates from different areas and different times within the facility were genetically related, as some of our data suggests. As a result of this study, the laundry facility implemented new protocols in an effort to reduce the level of contamination and potential for occupational exposure. 11 These protocols include the use of EPA registered disinfectants on high touch surfaces, guard rails to physically block clean carts from getting underneath soiled linen chutes, color coding of carts (certain colors are used only for soiled linen), providing additional PPE (such as gloves and face shields) available at the point of use, and clearly posted PPE donning and doffing guidelines. Further studies involving collection of health records of employees, including immunological function and other exposures would need to be done in order to characterize the risk of infection due to exposure in the laundry. Ideally an exposure limit to each of the three pathogens would be developed. This would help determine if the risk of exposure is high enough to warrant changes in the handling and transportation of soiled clinical linens.

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#### CDC updates "best practices" for

hospital laundry

As hospitals seek to control the scourge and excessive costs incurred by superbug outbreaks, all vectors of possible pathogen transmission must come under scrutiny. The processing of healthcare laundry is a complex operation, involving factors such as ventilation, transport, appropriate chemicals and equipment. Frequently, this task is outsourced to healthcare laundry services, and an increasing number of these facilities are proactively seeking certification or accreditation to ensure the highest possible standards. According to Nancy Jenkins, executive director of the American Reusable Textile Association, "training employees and clients in the proper handling and storage of linens is of paramount importance". Nonetheless, while many laundry services offer in-service training for the best practices in handling, clients have not been particularly receptive. Additional training may soon become mandatory.

In a <u>2015 review</u> (ICHE 36:1073-88), Lynne M. Sehulster of the CDC has set forth a compilation of the findings and recommendations of peer-reviewed studies on the handling of healthcare fabrics. View a <u>Q&A with Sehulster</u> and also high-lights of the CDC review in this <u>power point slide</u> presentation.

Roberts & Michael references continued...

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### **Upcoming Events**

#### February 23-25, 2017:

<u>Antimicrobials 2017</u> Australian Society for Antimicrobials 18th Annual Scientific Meeting. Adelaide, Australia

#### February 26 - March 3, 2017:

<u>Antimicrobial Peptides Gordon Research Conference.</u> Ventura, California

#### February 27, 2017:

7<sup>th</sup> Clinical Microbiology Conference. Amsterdam, The Netherlands

#### March 7-8, 2017:

Second Semmelweis CEE Conference, Budapest, Hungary

#### March 20-21, 2017:

SMI's 19<sup>th</sup> Annual Conference: Superbugs and Superdrugs - a focus on antibacterials. London, UK

#### March 22-25, 2017:

ASM Conference on Innovative Microbial Ecology for Mitigation of Antibiotic Resistance and Bacterial Diseases, Crystal City, VA

#### **April 22-23, 2017:**

Global Health and Innovation Conference.

Yale University, New Haven, Connecticut

#### **April 22-25, 2017:**

27<sup>th</sup> European Congress of Clinical Microbiology and Infectious Diseases (<u>ECCMID</u>). Vienna, Austria

#### June 1-5, 2017:

ASM Microbe 2017. New Orleans, LA, USA

#### June 14-16, 2017:

<u>Association for Professionals in Infection Control and Epidemiology (APIC) Annual Conference</u>. Portland, Oregon

**June 20 – 23, 2017:** <u>ICPIC 2017</u>, 4<sup>th</sup> International Conference on Prevention and Infection Control, Geneva Switzerland

#### July 31-August 01, 2017

<u>3rd World Congress and Exhibition on Antibiotics and Anti-biotic Resistance</u>; The Future of Antibiotics: Key Opportunities & Emerging Therapies. Milan, Italy

#### Sep 25, 2017

7th Annual Congress on Clinical Microbiology, Chicago, Illinois, USA

October 4 – 8, 2017: ID Week 2017, San Diego, California

## APUA in Action

### APUA informs media on superbug threats

- ♦ A recent Reuters investigation has detailed "the deadly epidemic America is ignoring" by recounting the story of a single transplant patient who received 14 different antibiotics, but ultimately died from six or more antibiotic-resistant infections acquired during hospital procedures. The article cites President Levy and APUA's 2009 study which estimated the overall cost of such hospital-acquired infections at over \$20 billion. The Reuters article outlines the hidden cost associated with infections that are rarely detailed in hospital reports, and emphasizes the lack of reliable data, which hinders efforts to calculate the actual cost. In its own investigation of more recent data from 2013, Reuters estimates that MRSA adds ~\$11,000 per inpatient stay and *C. difficile* adds ~\$5,200 accumulating to a national cost of \$6 billion for both.
- ♦ A <u>HealthDay</u> news article has summarized the latest U.S. government report (<u>JAMA Sept 20, 2016</u>) on the major public health problem posed by antibiotic-resistant bacteria and the need for a multipronged approach to address it. In a <u>HealthDay</u> news interview, President Levy commented, "Although there appears to be better awareness of the problem of antibiotic resistance among the public, recent surveys show that this knowledge has not yet translated into better antibiotic usage." He also emphasized the need for new antibiotics and the need to optimize older antibiotics that have fallen out of favor, but which could be resurrected to help alleviate the current resistance problem.
- ♦ As one of the early researchers who questioned the value of triclosan in home-based healthcare products, Levy was <u>interviewed by CNN</u> in its recent report on the topic of antibacterial chemicals in soaps. The article reviews the evidence and steps leading up to the recent FDA ban on 19 antibacterial chemicals in personal care products. As manufacturers could not provide the requested evidence to demonstrate safety and clear benefit, the proposed <u>FDA rule</u> will go into effect September 26, 2017.

## Tufts study revisited in *Scientific American* report

In a December 1, 2016 Scientific American article, "How drug -resistant bacteria travel from the farm to your table," reporter Melinda Mover documents her personal journey to a giant hog production farm in Indiana while investigating the evidence that farm antibiotic use had led to superbugs in our food. The article cites APUA President Levy's 1976 farm study of growth-promoting antibiotic use in chickens as the first evidence for the link between animals and humans. It then details subsequent compelling studies out of the Netherlands, and by Smith et al in Iowa (2013), and Price in 2012. The article notes that, while many farmers have abandoned antibiotics as "growth promoters" per se, some 70% or more of all hogs and cattle on U.S. feedlots, and 20-52% of chickens receive mass-feed antibiotics at some point in their lives under the guise of "disease prevention and control." Such use is still allowed under new restrictive FDA directives that became effective in Jan. 2017, and explains why the new ruling is unlikely to affect the overall use of antibiotics on U.S. farms.

The article goes on to document the generation of transmissible antibiotic resistance genes and the complex routes by which they end up in food products that make their way to the table and can ultimately cause resistant infections months or years later. She also demonstrates the difficulties in accessing industrial farms and the roadblocks encountered in performing the studies needed to definitively prove the cause and effect relationship between growth-promoting antibiotic use and the emergence of antibiotic resistant infections in humans.

### APUA-Nepal issues 13th Newsletter

APUA-Nepal has released its latest *Newsletter*, which features a comparison of clinical antimicrobial sensitivities from 2013 and 2016. The data cover major pathogens from blood, pus and urine isolates of the Tribhuvan University teaching hospital. The chapter also reports that it has been instrumental in crafting Nepal's 2016 National Antimicrobial Resistance Containment Action Plan.

## Antibiotic Resistance in the News

### Updates on superbug threats

CDC reports emergence of novel panresistant *Klebsiella* 

In late 2016, a woman who returned to Nevada following a lengthy stay in India, succumbed to sepsis caused by a carbapenem-resistant *Enterobacteriaceae* (CRE)—specifically, a *Klebsiella pneumoniae* that proved resistant to 26 drugs. The finding, reported in the <u>Jan 13, 2017 issue of Morbidity and Mortality Weekly News</u> is notable because it marks the first isolation in the U.S. of a New Delhi metallo-beta-lactamase element that resists colistin. CDC testing found susceptibility to fosfomycin, but the intravenous formulation needed for this infection is not currently available in the U.S. The study authors urge vigilence in obtaining travel histories on new hospital admissions and screening for CRE, plus strict infection control and contact tracing in the event of any NDM or *mcr-1* identification.

The report has precipitated a <u>January 18 op-ed article</u> in the New York Times, coauthored by Nicholas Bagley (Univ. of Michigan) and <u>APUA's 2015 Leadership Award winner</u>, Kevin Outterson (Boston Univ). In the face of a possible "post antibiotic era," coupled with projected staggering economic costs, the authors argue that current pharmaceutical and government initiatives are insufficient to halt the catastrophe. The current patent system is "not the right fit for antibiotics". Instead, they propose a "market-entry" reward system in the form of a substantial financial prize for manufacturers who can successfully bring an innovative, targeted antibiotic to market. In exchange, producers would surrender their patent. While lowering antibiotic costs and making them more accessible globally, the plan would admittedly be costly—estimated at \$4 billion per year.

Carbapenem resistance shows up on U.S. agricultural farm

The emergence of carbapenem-resistant *Enterobacteriaceae* (CRE) has seriously undermined our antibiotic arsenal. As the

carbapenems are not used in agriculture, the <u>finding</u> of a transmissible carbapenem resistance gene on a U.S. farm is both surprising and concerning. The carbapenem-coding bla<sub>IMP-27</sub> gene was recovered from multiple different environmental samples of a 1,500 sow farrow-to-finish family farm where no new animals had been introduced for 50 years. No pigs destined for slaughter were carriers. The gene is located on a highly transmissible plasmid with a wide host range and was found in multiple *Enterobacteriaceae* species from environmental samples of nursery and farrowing rooms, but not from feces. Study authors Thomas Wittum and team conclude that their findings imply a "real risk that CRE may disseminate in food animal populations and eventually contaminate fresh retail meat products."

Resistant gonorrhea — and no back-up plan

For the first time in the U.S., a cluster of gonorrhea strains in Hawaii has <u>emerged</u> with elevated resistance to the last antibiotic combo approved for treatment—ceftriaxone and azithromycin. As one of the CDC's three "urgent' antibiotic resistance threats, the pathogen is edging towards the 5% resistance cutoff frequency—the point at which the drugs will no longer be recommended. "We're talking in years, but not a lot of years," says Alan Katz, director of the Hawaii Diamond Head STD Clinic where the resistances were found.

A dry antibiotic pipeline, coupled with diminished testing and the dismantling of public health clinics is believed responsible for the continued rise in drug-resistant gonorrhea. In the 1990's, the CDC abandoned MIC testing in favor of a faster, simpler genetic diagnostic that did not include drug susceptibility. With the exception of Hawaii, fewer than 5% of all gonorrhea cases are currently tested in the U.S.

The solution to the problem appears to lie with newer drugs and novel diagnostics, such as Entasis's ETX0914 antibiotic, which is performing well in clinical trials, and also with a new

<u>molecular assay</u> aimed at detecting strains that will respond to an older, currently abandoned antibiotic, ciprofloxacin.

## Polluted Beijing air carries antibiotic resistance genes

APUA *Newsletter* author (<u>Vol 34,#2</u>) Joakim Larsson and his Dutch research team have <u>found high levels of antibiotic resistance genes</u> in the heavily polluted air of China's capitol, Beijing. The deeply sequenced air samples revealed 64 types of antibiotic resistance genes—including genes coding for resistance to the "last resort" carbapenem antibiotics. As the research methodology used could not determine bacterial via-

bility, the extent of risk to human health is yet undetermined. But Larsson notes that "It is reasonable to believe that there is a mixture of live and dead bacteria, based on experience from other studies so far." The reports caused widespread panic among Beijing residents, leading authorities to delete online news reports and downplay the alarm.

Larsson's team is planning studies of air composition at sewage treatment plants and of gut bacteria from plant workers

and nearby residents in order to search for links between the two.

Australian hospitals report shortages of first-line antimicrobials

Australian infectious disease doctors have <u>reported the shortage</u> of three highly effective, affordable and least toxic antimicrobials: the antibiotics vancomycin and metronidazole, and Acyclovir — an antiviral. As none of the drugs are produced domestically, Australians are totally reliant on sourcing from around the world. Doctors were caught off-guard with the unexpected announcement, which allowed no time for planning.

Australia treats about 500 superbug infections per year, with

vancomycin being a critically important treatment for MRSA. With vancomycin in particular, the alternative options are quite limited. According to Professor John Turnidge, head of Australia's national antimicrobial and antibiotic resistance surveillance program, "We can use what we call the 'last-line' box of antimicrobials, which we reserve for cases of resistance with vancomycin, but if we use them widely they'll be useless as well." In addition, the use of broader spectrum drugs can pose complications such as bowel inflammation, with greater risk of infection to the community.

According to Pfizer, the manufacturer of metronidazole and

vancomycin, the shortage was due to "increased demand as a result of other manufacturers and distributors exiting the market or experiencing their own supply disruptions on their medicines". The problem is compounded by the fact that Australia's Therapeutic Goods Administration (TGA) approves only one manufacturer to import a specific drug.

British study itemizes cost of superbug outbreak at one million pounds (\$1.2 million U.S.)

In 2015, five West London hospi-

tals were afflicted with a 10-month outbreak in which 40 patients in renal and vascular wards were infected with a carbapenemase-producing strain of *Klebsiella*. Thirteen patients died. An investigative team from Imperial College London has now <u>calculated the staggering cost</u> of this antibiotic resistance outbreak at £980,000. The greatest cost (£296,000) turned up as lost revenue from planned surgical procedures that were cancelled due to the closure of four wards. Other major expenses were extra staff time (£193,000), extended patient length-of-stay (£140,000), and patient screening (£84,000). Twenty-four rooms required hydrogen peroxide vapor decontamination (£37,000). According to lead author, Alison Holmes, "This study highlights the cost to the British NHS

## **CDC's "Winnable Battles" report** notes improving trends

The U.S. Centers for Diseases Control has noted the following five improvements in healthcare-associated infections between 2006 and 2014:

- ◆ A **50% decrease** in central line-associated bloodstream infections (between '08 and '14)
- ◆ A 13% decrease in hospital-onset MRSA bacteremia (from '11-'14) and a 36% decrease in HA- invasive MRSA (between '08 -'14)
- ♦ A 17% decrease in certain surgical site infections
- A decrease of 8% in C-diff infections ('11-'14)
- ◆ A 16% and a 24% decrease in catheter-acquired UTI in hospital intensive care units and acute care hospital wards respectively. ('09 -'14)

and why a relatively small investment in infection prevention strategies could save money in the long term."

### Advances in Technology

FDA clears a one-hour test for MRSA colonization detection

Cepheid's most recent rapid diagnostic—Xpert® MRSA NxG—has recently received U.S. FDA clearance. The next-generation test is an accurate, on demand molecular diagnostic that delivers results in ~1 hour. It was developed using a library of a global, more inclusive range of MRSA strains — including mecA and mecC strains— thereby reducing the frequency of false-positive results that occur from "empty cassette" strains. The test is expected to improve MRSA surveillance, which has been instrumental in reducing the spread of MRSA in healthcare settings, in decreasing days in isolation, and lowering hospital costs.

## Chinese scientists succeed in synthesizing Teixobactin

With more than 15 research teams competing around the globe, Chinese scientists from Hong Kong polytechnic University and The University of Central Florida have recently reported success in chemically synthesizing the naturally derived antimicrobial, teixobactin, which was isolated from soil bacteria in early 2015. Because of teixobactin's broad-range activity against such critical pathogens as MRSA, vancomycinresistant enterococcus and *Mycobacterium tuberculosis*, coupled with its projected failure to develop antibiotic resistance, the compound has generated global excitement as a 'gamechanging' antibiotic. To date, the Chinese research team has successfully generated 10 promising teixobactin analogs and aims to synthesize 100 more within the next two years in search of compounds with improved pharmacological properties that can be developed into viable antimicrobials.

Novel approaches help revive older antibiotics

Up to 20% of patients infected with MRSA die from systemic infections due to its highly virulent toxin genes. In attempts at reviving older antibiotics to confront the antibiotic resistance problem, scientists from the National University of Galway and the University of Liverpool have teamed up to demonstrate

### Publications of Interest

- <u>FAQs on antibiotic myths: the author responds.</u> 2016.
   Brad Spellberg, MD responds in depth to readers' questions following his October 16, 2016 Medscape article, *Antibiotics: 5 myths debunked*.
- <u>Community-acquired methicillin-resistant Staph aureus</u> (Ca-MRSA) infections pipeline review H2 2016.

  Produced by Global Markets Direct, this guide provides comprehensive information, including current and emerging key players, on therapeutics under development for CA-MRSA.
- Nasal decolonization and HAI prevention: applications and evidence. Infection Control Today Dec 12, 2016 S.
   Barnes describes and grades the supporting evidence for nasal decolonization strategies using mupirocin and alternative nasal antiseptics.
- WHO's <u>Global Tuberculosis (TB) Report 2016</u>. An annual update on progress in prevention, diagnosis and treatment.
- <u>Community- and healthcare-associated methicillin-resistant Staphylococcus aureus strains: and investigation into household transmission, risk factors, and environmental contamination.</u> W Ng et al. examine transmission from index cases of MRSA-colonized or infected case patients to household members, pets and high-use environmental locations and associated risk factors. Infect Control Hosp Epidemiol 2016 8:1-7
- Resistance Open—is an online platform developed by D.R. MacFadden et al. for aggregating and describing anti-microbial resistance and promoting global surveillance.
   J Infect Dis. (2016) 214: S393-S398
- Antimicrobial Stewardship: Managing Antibiotic
  Resistance". This massive, open online course (MOOC)
  covers antibiotic prescribing within all health economies
  internationally, and is considered to be a "...valuable
  beginning for extending education on antimicrobial
  stewardship..." British Society for Antimicrobial
  chemotherapy and the University of Dundee MOOC.
  (starts Feb 27)
- Will 10 million people per year die due to antimicrobial resistance by 2050? This Plos Medicine Essay (Nov. 29, 2016) by M. deKraker et al. challenges the oft-cited estimate and discusses the need for improved surveillance that can better support long-range predictions.

#### Publications of Interest continued...

- <u>A diverse intrinsic antibiotic resistome from a cave</u>

  <u>bacterium.</u> A.C. Pawlowski et al. use multiple methodologies to show the remarkable genotypic and phenotypic diversity of a highly resistant *Paenibacillus* sp. that has persisted for millennia. Nature Communications (2016)
- <u>Community-acquired pneumonia in the Asia-Pacific region.</u>
  J. H. Song *et al.* discuss antimicrobial manage-ment and the unique situation posed by the high incidence of *Klebsiella* and *Burkholderia pseudomallei* in the Far East. Semin Respir Crit Care Med (2016) 37: 839-54
- Antimicrobial stewardship in the emergency department.:

  Challenges, opportunities, and a call to action for pharmacists. This review article by B.M. Bishop highlights successful interventions that have curbed antibiotic use in the ED setting and proposes newer, as-yet unvalidated, measures.

that penicillin can weaken the virulence of these bacteria, even though it does not kill them. The scientists showed that penicillin causes the bacteria to switch off toxin production in favor of building cell wall components that counteract the antibiotic. Once the cells are compromised, the body's natural immune system can defeat the infection—sometimes coupled with an additional antibiotic. For example, a recent clinical study in Australia showed that MRSA sepsis could be significantly reduced from 3 days down to 1.9 days by using the beta-lactam flucloxacillin in combination with vancomycin. The findings suggest potential changes in the way MRSA infections will be handled in both hospital and community settings.

In a completely different approach, <u>reported</u> in the *Journal of Antibiotics*, Charles Rice and team at Oklahoma University restored the susceptibility of MRSA to ampicillin by adding a polymer [branched poly(ethylenimine), BPEI] to the antibiotic. The newly patented formula prevents teichoic acid synthesis in the bacterial cytoplasm, which is responsible for the resistant bacterial cell wall. The implications are that other penicillin-type drugs can be combined with BPEI or related polymers to create new first-line antibiotics against multiple different pathogens.

For an APUA feature article on revitalizing older antibiotics, see 2016 Vol 34(2): Optimizing the Use of Old Antibiotics — A Global Health Agenda

#### Antimicrobial peptides in the news

Two newly synthesized antimicrobial peptides show promise in their ability help to overcome the weak killing capacity that has limited use of their naturally occurring counterparts. In one approach, MIT scientists have teamed up with researchers from Brazil and British Columbia to engineer the naturally occurring antimicrobial peptide, clavanin-A, making it more effective against multidrug resistant-strains of *Staphylococcus aureus* and *E. coli*. With the addition of a five amino acid sequence, the new peptide, named <u>clavanin-MO</u>, is more hydrophobic and therefore, more efficient at poking holes in the pathogen's cell membrane.

Using an alternative synthesis, scientists from London have developed the novel peptide, <u>Tilamin</u>, which effectively "peels" the outer bacterial membrane of the target pathogen. Unlike classic antimicrobial peptides, which bore a hole straight through the membrane, Tilamin takes an angular approach through one layer of phospholipids, exposing the hydrophobic tails of the inner membrane. The multiple holes expand and merge, resulting in membrane disintegration.

Scientists envision such novel peptides can be embedded in surfaces to form antimicrobial coatings or ointments that resist microbial biofilm production.

For an APUA feature article on antibacterial peptides, see <u>Vol 34(1):</u> <u>Bacteriocins: peptide antimicrobials with therapeutic promise</u>

Urban dirt bacteria yield promising medical compounds

Researchers are now finding and exploiting potentially valuable genes from the multitude of diverse, unculturable urban microbes that thrive in such sites as New York City's Central Park and subway systems, and on automatic teller machines. In a metagenomics study of soils from multiple city parks, Rockefeller University biologists screened composite bacterial sequences for clusters of genes that are related to clinically important treatments. Among the two dozen they found was the genetic signature of an antibiotic named tiacumicin. According to research team director Sean Brady, there is an abundance of unfamiliar genes in local microbiomes that may be equally or more productive than those found in exotic environments.



## "Preserving the Power of Antibiotics" ®

### About us

Antibiotics are humanity's key defense against disease-causing microbes. The growing prevalence of antibiotic resistance threatens a future where these drugs can no longer cure infections and killer epidemics run rampant. The Alliance for the Prudent Use of Antibiotics (APUA) has been the leading global non-governmental organization fighting to preserve the effectiveness of antimicrobial drugs since 1981. With affiliated chapters around the globe, we conduct research, education and advocacy programs to control antibiotic resistance and ensure access to effective antibiotics for current and future generations.

Our global network of infectious disease experts supports country-based activities to control and monitor antibiotic resistance tailored to local needs and customs. The APUA network facilitates the exchange of objective, up-to-date scientific and clinical information among scientists, health care providers, consumers and policy makers worldwide.

The APUA Newsletter has been published continuously three times per year since 1983. Tel: 617-636-0966 • Email: apua@tufts.edu • Web: www.apua.org

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