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Resistant Microbes; an EAC White Paper

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The Threat

Antibiotic resistant bacteria have been a problem since the dawn of the antibiotic era, however pleas for judicious antibiotic use have largely fallen on deaf ears. It is only recently, more than 70 years after the discovery of penicillin, that the multi-drug resistant microorganisms (MDRO) finally got some respect and widespread attention. A CDC report[1] estimates that, "*Each year at least two million illnesses and 23,000 deaths are caused by antibiotic-resistant bacteria in the United States alone*." The CDC also reports that there are "*at least $20 billion in excess direct health care costs and up to $35 billion in lost productivity due to hospitalizations and sick days each year*." Statistics in a UK study[2] are pessimistic; the study estimates that, "*continued rise in resistance by 2050 would lead to 10 million people dying every year and a reduction of 2% to 3.5% in Gross Domestic Product (GDP). It would cost the world up to 100 trillion USD*." A New York Times[3] article is concerned that the resistant organisms being bred in India will spread, describing "*a deadly epidemic that could have global implications is quietly sweeping India, and among its many victims are tens of thousands of newborns dying because once-miraculous cures no longer work.*" The New York Times article also reports that "*nearly a third of the world's newborn deaths occur in India*," and that many infants are *"born with bacterial infections that are resistant to most known antibiotics, and more than 58,000 died last year as a result*." Further, that "*the rising toll of resistant infections could soon swamp efforts to improve India's abysmal infant death rate*."

National Policy

The US government is appropriately concerned and has issued a National Action Plan[4] (NAP) in which it would like to: "*(1) Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections, (2) Strengthen National One-Health Surveillance Efforts to Combat Resistance, (3) Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria, (4) Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines, and (5) Improve International Collaboration and Capacities for Antibiotic-Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development*."

[1] *Fact Sheet: President's 2016 Budget Proposes Historic Investment to Combat Antibiotic-Resistant Bacteria to Protect Public Health*; CDC, *Antibiotic Resistance Threats in the United States, 2013*.

[2] *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations, The Review on Antimicrobial Resistance Chaired by Jim O'Neill*, December 2014.

[3] Gardiner Harris, 'Superbugs' Kill India's Babies and Pose an Overseas Threat, *New York Times*, December 3, 2014.

[4] The White House, *National Action Plan for Combating Antibiotic-Resistant Bacteria*, March 2015.

Healthcare Challenge

Healthcare arrives on this scene with imperfect tools, increasing regulatory demands, and financial burdens in the form of excessive costs for hospital-acquired infections and financial penalties for certain healthcare associated complications. In the US National Action Plan, NAP-1, nationwide implementation of anti-microbial stewardship (AMS), is a good and logical requirement. Unfortunately, traditional microbiology, with its 1-3 day delivery of microbial identification and sensitivity information (ID/AST), is wholly inadequate to fulfill NAP-2. NAP-3 is a bugle call to the diagnostic industry, as NAP-4 is for the pharma sector. Finally, NAP-5 is a plea to the world, but especially to unnamed countries like India, issued in the hope that they will reign in their unrestrained use of antibiotics – precisely the practices that create the environment in which MDROs can rapidly develop. Unfortunately, hope is not a plan. In other words, these five assignments are a tall order leaving plenty of room for improvement.

Hopeful Solutions

In EAC's view, there is also reason for optimism within US healthcare in (1) new diagnostic (Dx) technologies, (2) new, narrow spectrum antibiotics (Rx), (3) healthcare network plans to implement real-time infection detection and prevention systems, and (4) network integration in US healthcare. This optimism is tempered with the financial realities faced by healthcare; the adoption of newer tools and strategies is a permanent challenge until superior cost and medical benefits are demonstrated.

New diagnostic technologies

EAC has interviewed respected Infectious Disease (ID) physicians in the US and Europe and found that these ID clinicians desired faster organism identification and AST determination more than anything else. Knowledge regarding an organism's antibiotic susceptibility is the most critical piece to ensure timeliness of appropriate therapy and to rapidly transition away from broad-spectrum antibiotics. These antibiotics not only select for resistant bacteria but disrupt the healthy gastrointestinal bacterial population. In their view, pathogen ID could wait, but AST could not. This observation is also in agreement with the experience of Dr. John Burke[5]. Fortunately, in other studies, EAC identified (and is tracking) a number of technology companies developing ID/AST microbiology systems with six-hour or shorter sample-to-answer turn-around times, placing the challenge of a one-hour ID/AST system within realistic reach. EAC has also conducted retrospective clinical studies in the area of other rapid Dx areas, such as a rapid sepsis test. In EAC's observation, new rapid molecular Dx technologies are likely to be available in the near-term of three years. As offered before, financial considerations will remain a challenge for adoption of newer, more expensive tests until medical and economic benefits have been proven.

New narrow-spectrum antibiotics in Pharma

EAC is aware of a number of efforts by Rx companies to develop pathogen-specific antibiotics; most with claims for a new mode of action. EAC itself has been contacted by two pharma companies for project plans to conduct large-scale retrospective clinical studies to determine the impact and optimal deployment of such drugs based on their intrinsic economic and medical value. Dr. David Pombo has prepared just such a study plan for one in early 2015. In EAC's observation, new, narrow-spectrum antibiotics are likely to be available in the near-term of perhaps three years. It goes without saying that the new drugs will need to be guarded by effective antimicrobial stewardship

[5] John Burke, MD FACP, FIDSA, EAC Senior Medical Advisor, Chief, Department of Clinical Epidemiology and Infectious Diseases, Intermountain Healthcare, Salt Lake City, Utah.

programs in the developed countries. Further, some yet to be defined international efforts to prevent what has been observed about resistant organisms being bred in India are needed.

Real-time infection detection of resistant organisms and prevention systems at healthcare networks

The ultimate benefit of rapid detection is rapid prevention, reduced transmission and better treatment. Detecting resistance alone (NAP-3 goal) however is of little importance without the means to disseminate the information rapidly for action and to efficiently and effectively conduct surveillance for resistant organisms (NAP-2 goal). In EAC's view, tightly-integrated care-continuum networks are likely to be the first to design and install network-wide, real-time, ID detection and prevention systems, because it will take the substantial resources of such networks to define the design parameters and prepare the required investment and return analyses.

The goals for such a system are seen as the optimization of laboratory and clinical workflow, establishment of support from experts in Infectious Diseases (e.g. ID physicians or ID trained pharmacists), monitoring the proper execution of Rx administration, tracking the emergence and spread of MDROs, and practice effective network wide AMS. For purposes of illustration, these observations are in line with goals set for a network-wide project by Dr. Bert Lopansri. EAC is in the process of conducting a large-scale retrospective clinical study[6] within a large integrated network. The goal of the study is to lay the foundation that can be used to establish a command and control system by defining the burden of resistance as well as the gaps in resistance detection and reporting posed by traditional microbiology methods. This study is sponsored by a Dx company client, which has sophisticated molecular ID/AST technologies paired with a robust software/bioinformatics tool to enhance surveillance for MDROs. Subsequent studies are likely to arise from this collaboration, which include prospective clinical studies directed by retrospective study results. EAC believes that the future for preventing antibiotic resistance requires careful coordination between multiple care teams that starts with detecting an MDRO in a clinical laboratory. This poses great challenges to individual hospitals but can be more easily solved with a network-wide command and control system available to integrated networks.

Hospital integration in US healthcare

In various client studies in the past two years, EAC identified a trend in the emergence of integrated networks[7]. A byproduct – whether intended or not – of the Affordable Care Act (ACA), and its Accountable Care Organization (ACO) concept was a notable acceleration in the formation of tightly integrated networks (ownership, corporate governance). EAC has projected that by 2025 there will be nearly 370 such networks, and that they will own almost 4,200 of the roughly 5,200 hospitals in the US, along with some 21 to 23,000 owned or contracted physician groups.

[6] The study will describe the global burden of antibiotic resistant bacteria in an integrated healthcare system over a seven year period from 2008 to 2015, to determine the incidence and prevalence of patients who have tests or cultures positive for Clostridium difficile, Extended-spectrum beta-lactamase producing (ESBL) Escherichia coli, ESBL Klebsiella pneumonia, Vancomycin resistant Enterococcus faecium (VRE), Methicilin resistant Staphylococcus aureus (MRSA), Carbapenem resistant Escherichia coli and Klebsiella pneumoniae (CRE), multidrug resistant Acinetobacter baumanii, multidrug resistant Pseudomonas aeruginosa, and multidrug resistant Enterobacter sp. The goal is to describe the likely origin of antibiotic resistant bacteria (hospital acquired vs. community acquired) and changes in incidence and prevalence over time; year over year.

[7] Most recently in a mid-2015 study managed by Susan Farber, EAC COO and President.

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Already in 2014, there were some 11 national and 300 other tightly integrated networks[8], which went beyond acute care to acquire multiple layers of care. This includes ambulatory care facilities, visiting nurse arms, and even "*mall medicine*." In EAC terminology, the multiple layers of care made these networks "*care-continuum*" networks. In the view of Dr. Bert Lopansri, of key importance is the existence of integrated networks that have a robust, electronic clinical data infrastructure, such as Intermountain Healthcare[9], and can use their own data to identify gaps and implement change to improve the quality of care. In other words, tight network integration allows for systems to determine if new diagnostic and screening tools are needed in the quest to prevent development and spread of antibiotic resistant bacteria and can contribute substantially to the ambitious goal established by NAP-5. Integration is also seen in the CDC's efforts to promote multi-facility collaborations.[10]

In summary

In EAC's view, it may turn out that healthcare itself is the best driver for the required developments in diagnostic technologies to combat the MDRO threat. More specifically, the tightly integrated care-continuum networks might be the ideal and appropriate agency to collaborate with pharma and diagnostic companies to guide specific product development and pipelines, develop and implement the appropriate detection and therapy-administration system, and build the required, matching AMS. If an adequate number of network and Rx/Dx companies participate, the combined efforts might just be the key to NAP-1 (slow the emergence of resistant bacteria), NAP-2 (strengthen surveillance), NAP-3 (develop innovative Dx), and NAP-4 (develop new antibiotics). NAP-5 is largely beyond the reach of healthcare, but there is evidence of newfound urgency by governments.

EAC believes that there is ample room for optimism.

[8] Sanofi, *Managed Care Digest Series, Hospital/Systems Digest 2015*.

[9] Intermountain Healthcare, 36 State Street, Salt Lake City, UT. A not-for-profit system of 22 hospitals, 185 clinics, a Medical Group with some 1,400 employed physicians, a health plans division called SelectHealth, and other health services.

[10] CDC, Make Health Care Safer, *Vital Signs*, August 4, 2015. http://www.cdc.gov/vitalsigns/stop-spread/