Sharing Knowledge, Achieving Breakthrough Performance:

The Multidrug-resistant Organism Repository and Surveillance Network

Introduction:

Antimicrobial resistance in bacterial pathogens is steadily increasing and recognized as one of the greatest threats to global public health. Very few drugs with activity against Gram-negative multidrug-resistant organisms (MDRO) have been brought to market. Fewer still are expected in the foreseeable future. Many medical advances that physicians and patients take for granted - including cancer treatment, transplantation, surgery, and neonatal care - are endangered by increasing antibiotic resistance and the distressing decline in antibiotic research and development. Infections with MDRO increase healthcare costs, morbidity, and mortality.

Shortly after the beginning of the wars in Afghanistan and Iraq, the Military Health System (MHS) experienced a major increase in wound and healthcare-associated infections caused by MDRO with extremely limited treatment options. In addition to complicating the care of wounded service members, MDRO have spread to and killed civilian healthcare beneficiaries hospitalized in the same facility as combat casualties. Furthermore, transmission of MDRO from a war-wounded patient to a healthcare worker resulting in a prolonged, near fatal infection, and a similar father/daughter transmission has now been reported. Many MDRO are resistant to all available antibiotics, making adequate therapy difficult or impossible to achieve.

Therefore, numerous civilian and military agencies and professional societies have called for intensified, novel responses to the antibiotic resistance crisis. The Healthcare Infection Control Practices Advisory Committee and the CDC issued recommendations for specialized monitoring and reporting of MDRO. Additionally, the design and implementation of a National MDRO Surveillance Plan has been deemed a 'Top Priority Action Item' by the Interagency Task Force on Antimicrobial Resistance. Because MDRO spread has been linked to intercontinental travel, and because wounded service members often pass through 4-5 geographically diverse hospitals during initial treatment and evacuation, global approaches are especially relevant for the MHS.

Against this backdrop, we launched the Multidrug-resistant organism Repository and Surveillance Network (MRSN) in 2009. Although surveillance and monitoring for emerging resistance in MDRO has been advocated for decades, there was no enterprise-wide effort to capture and centralize the microbiological and molecular-epidemiologic data necessary to inform and focus infection prevention and control in the MHS before the MRSN.

Its objective and mission is to collect and characterize MDRO across the MHS enterprise to inform, enhance, and focus clinical practice, healthcare policy, and infection control efforts. It collaborates with the IPCP *, NMCPHC*, AFHSC*, PHC*, GEIS*, HPA-ARMRL*, and the CDC*. (*spelled out below)

The MRSN provided valuable infection control support, especially to unstable areas such as Afghanistan, Iraq, and post-earthquake Haiti. It determined sources of outbreaks, facilitated life-saving interruptions of nosocomial transmission and influenced surveillance and antibiotic stewardship policies. It was the first to detect the emergence of important drug resistance genes in the MHS and in the U.S. Early accomplishments culminated in winning first place for the 2010 Excalibur award. The MRSN is looked to as a model by the Infectious Diseases Society of America. Army Medicine has taken a clear lead by authorizing and supporting this initiative, which has no counterpart in the DOD or the civilian-private sector.

Methods:

Garnering the endorsements and concurrences of microbiology and infectious diseases consultants to the Surgeon General was also required. Central to the uniqueness and success of the MRSN was garnering an OTSG-MEDCOM mandate directing Army hospitals to submit isolates with personal identifiers, namely Policy memoranda 90-050 (June 2009) and 11-035 (April 2011). Air Force and Navy hospitals participate voluntarily. However, the Air Force Surgeon General has recently directed his Infectious Diseases Consultant to begin implementation.

Hospital laboratories submit all targeted MDRO, with clinical and demographic information, to the laboratory at the Walter Reed Army Institute of Research. The repository determines genetic relatedness, performs extended resistance and molecular analyses, and relays clinically relevant information to hospitals, medical leaders, and policymakers.

More specifically, isolates undergo: 1) confirmatory antibiotic susceptibility testing on all three of the most widely used commercial susceptibility testing systems, 2) pulsed- field gel electrophoresis to determine strain relatedness, 3) optical genome mapping and sequencing to determine how MDRO strains are sharing and transferring mobile genetic elements that increase resistance or virulence, and special molecular assays for the presence of emerging genes or genetic elements that destroy broad spectrum antibiotics (referred to as "super bug genes"), and 4) archival cryopreservation.

Clinical and demographic information are combined with laboratory analyses into customized, event-driven reports, such as strain relatedness among patients and locations. These reports are sent to clinicians, infection control

teams, and policy makers to guide empiric therapy and enhance outbreak or emerging pathogen detection. Regular reports, such as monthly antibiograms, are also produced and distributed through Army Public Health Command venues and media. Ultimately, when the MRSN is fully mature, antibiograms and reports will be posted on a secure website and readily available to all clinicians 24/7. Network personnel conduct site visits to support isolate collection and provide actionable information to hospital infection preventionists, identifying potential outbreak strains and originating sources and patterns of transmission.

The network is currently targeting methicillin-resistant *Staphylococcus aureus* (MRSA) and multi, extreme, and pan-drug resistant *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. It is also adding molecular screening of MRSA isolates for the presence of antiseptic resistance genes (e.g., qac A/B), that can actually promote the growth of bacteria in commonly used disinfectants, such as chlorhexidine and mupirocin.

The MRSN works closely with the Tri-Service Infection Prevention and Control Panel (IPCP), The Navy and Marine Corps Public Health Center (NMCPHC), Armed Forces Health Surveillance Center (AFHSC), the Public Health Command (PHC), the DOD Global Emerging Infection Surveillance and Response System, (GEIS), the Joint Trauma System, U.K.'s Health Protection Agency-Antibiotic Resistance Monitoring & Reference Laboratory, (HPA-ARMRL), and the Centers for Disease Control and Prevention (CDC). For improved data comparison and information sharing, all of the methods and protocols the MRSN uses to determine which strain relatedness are identical to those used by the CDC. The MRSN is currently initiating collaborations with the National Institutes of Health and the Department of Veterans Affairs.

Results:

Currently, 13 military treatment facilities (MTFs), including 5 in war zones, are enrolled and actively participating. To date, over 3500 bacterial isolates have been received in the MRSN laboratory, with almost half of those fully characterized and archived. Included in those are over 1000 extremely drug-resistant bacteria that were screened for the presence of the recently emergent NDM-1 gene from New Delhi, India (which confers resistance to nearly all available antibiotics and has caused several deaths globally). The MRSN was the first to detect emergence of this gene in Afghanistan, in the MHS and in a new species. Additionally, infectious disease outbreak assistance was requested 14 times from 6 MTFs, including combat support hospitals in Iraq and Afghanistan, the USNS Comfort while deployed in support of the Haiti earthquake, Landstuhl Regional Medical Center, Navy MTFs in

Spain and Guam, for a fatal MRSA outbreak in the Neonatal Intensive Care Unit (NICU) at the National Naval Medical Center (NNMC) (Bethesda), and most recently for a cluster of colistin-resistant (the drug of 'last hope') *Acinetobacter* infections of wounded warriors at and Walter Reed National Military Medical Center. Turn-around time from request for laboratory assistance to feedback of actionable information ranged from 3.5 days for MTFs in the National Capital Region to13 days for the USNS Comfort stationed in coastal Haiti during the earthquake. Of note, turnaround time even for the most challenging organisms was similar to, or faster than that of the most commonly used reference laboratories. Feedback from the MRSN resulted in intensified disinfection, temporary unit closures, restrictions on antibiotic usage (colistin), and changes in surveillance policies or protocols. Nosocomial transmission of a clone of MRSA involved in a fatal healthcare associated infection was successfully interrupted as was a cluster of hospital / ventilator associated pneumonia believed due to a contaminated bronchoscope.

Conclusion:

In its short two year existence, the MRSN achieved breakthrough performance by delivering its knowledge and analysis products to deployed and fixed facilities throughout the MHS. The MRSN utilizes state of the art technology (optical genome mapping and sequencing) as a tool to discover important differences among samples that would have been missed or disregarded. It promotes evidence-based practice by modeling its standard operating procedures after well-documented high-return-on-investment initiatives such as the Duke Infection Control and Outreach Network. The MRSN is adaptable, easily replicable, and can be readily transitioned to other like organizations. Indeed, it is being implemented across all three services at all echelons of care. The MRSN is outcome-based with measurable results and cost-avoidances, such as reduced healthcare-associated infections. Based on past performance, the MRSN is capable of maintaining results over time. Written guidance of ongoing review and evaluation of the process is available in the form of monthly customer stakeholder and customer solicitations for improvement suggestions that accompany each monthly MDRO bulletin. All of the collaborating agencies or organizations mentioned above (AFHSC, PHC, etc) have been receiving monthly MDRO reports since 2010. The MRSN has helped reduce the likelihood of infection and illness through focused prevention and increased awareness. It has unburdened enrolled MTF clinical laboratories of outbreak investigations and is informing clinicians and medical policy leaders for clinical management, therapeutic, and resource allocation decisions.

The MRSN is the first independent and sustainable centralized laboratory-based infection control and prevention program in the DoD. Its early successes culminated being awarded first place in the 2010 Excalibur award. Its mission is process-oriented by centralizing laboratory studies and interfacing with the clinical management of patients in the medical evacuation chain. The program was developed in conjunction with the full spectrum of MEDCOM stakeholders, to include health care providers, consultants to the Surgeon General, infection preventionists, and information management personnel. Output from the MRSN benefits all medical disciplines and subspecialties and includes any person who prescribes antibiotics, performs infection control or establishes healthcare policy.

Similar infection control initiatives similar are documented in the medical literature to decrease length of hospital stays, reduce antibiotic treatment, and improve patient outcomes. One such measurable event for the MRSN was the intervention described in the 'Results section' at the NICU at NNMC. As quoted by the Infection Control officer, “Due to near real time feedback from the MRSN, there was an immediate re-location of infants in the NICU, an intensified and repeat terminal cleaning of the pods that housed the affected infants, and the implementation of a new infection control policy wherein all admissions to the NICU are now actively screened for MRSA.” According to one Infectious Disease clinician at NNMC, "It is totally plausible that without feedback from the MRSN, nosocomial transmission of the MRSA strain would have continued, resulting in increased morbidity and more lives lost.”

Published data also captures the savings of life and resources described above. One showed a 23% -40% reductions in nosocomial bloodstream infections and ventilator-associated pneumonia, yielding potential savings of $500,000- $2.1million per year. Extrapolating this data over the next 3 years, it is predicted that the MEDCOM will realize a prevention of infection and/or death in 33 in-patients and a cost savings of $1.7-6.5 million. Conversely, for each MTF not under MRSN surveillance, the risk of avoidable infection related morbidity and mortality is predicted to include up to three additional patients, at a cost of $500K at each un-enrolled MTF. Similar literature-based projections suggest the MEDCOM will realize an overall return on investment of $5 for each $1 resourced to the MRSN.

The MRSN is aligned with the 10 prioritized capabilities for Joint Force Health Protection; specifically, emerging mission sets and medical communications and information management. In September 2010, the MDRO crisis has garnered congressional interest. All three infectious diseases consultants to the Surgeons General, and the Office of

the Assistant Secretary of Defense for Health Affairs were summoned before the House Armed Services Subcommittee on Oversight and Investigations to explain the MHS response to the MDRO crisis. All agreed that the MRSN should be officially expanded across all three Services. Army Medicine has taken a clear lead by authorizing and supporting this initiative, which has no counterpart in the DoD or the civilian-private sector.