The Antimicrobial Resistance Monitoring and Research (ARMoR) Program: The US Department of Defense Response to Escalating Antimicrobial Resistance

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(See the Editorial Commentary by Doron and Boucher on pages 398–400.)

Responding to escalating antimicrobial resistance (AMR), the US Department of Defense implemented an enterprise-wide collaboration, the Antimicrobial Resistance Monitoring and Research Program, to aid in infection prevention and control. It consists of a network of epidemiologists, bioinformaticists, microbiology researchers, policy makers, hospital-based infection preventionists, and healthcare providers who collaborate to collect relevant AMR data, conduct centralized molecular characterization, and use AMR characterization feedback to implement appropriate infection prevention and control measures and influence policy. A particularly concerning type of AMR, carbapenem-resistant Enterobacteriaceae, significantly declined after the program was launched. Similarly, there have been no further reports or outbreaks of another concerning type of AMR, colistin resistance in Acinetobacter, in the Department of Defense since the program was initiated. However, bacteria containing AMR-encoding genes are increasing. To update program stakeholders and other healthcare systems facing such challenges, we describe the processes and impact of the program.

Keywords. antimicrobial resistance; surveillance; infection prevention; Department of Defense.

The US response to escalating antimicrobial resistance (AMR) has been described as sluggish and more than a decade behind national organizations elsewhere, such as the European Union [1]. In an effort to close that gap and provide safe, high quality care, the US Department of Defense (DoD) launched the Antimicrobial Resistance Monitoring and Research (ARMoR) Program in 2009. It consists of an integrated network of policymaking and hospital-based infection preventionists, individual healthcare providers, research microbiologists and bioinformaticists, epidemiologists, and senior healthcare leaders. The program is government funded and thus includes all US taxpayers as stakeholders. To update these stakeholders, and because other healthcare systems may find part or all of the approach applicable to their efforts, we describe the program’s processes and highlight its impact.

METHODS

Policy Development
In the DoD, the offices the surgeons general of the respective military services establish medically related policies. Senior infection prevention and control and infectious diseases advisors provide expert guidance and recommendations (arrow A in Figure 1). At the regional and
local levels, hospital commanders can also establish and enforce local policy, but hospital commanders must adhere to any policy set forth by their respective military medical leadership. The backbone of the program is an Army infection control–quality improvement policy mandating the collection and characterization of targeted multidrug-resistant (MDR) bacteria. Medical informatics developed and applied by the Navy Antimicrobial Surveillance System and Navy–Marine Corps Public Health Center’s EpiData Center Department (hereafter “Navy”) complement and reinforce this mandate. (A copy of this policy is available from the corresponding author.)

Policy Execution
Now a multidisciplinary effort able to support the entire DoD, the ARMoR Program began as 2 separate entities: the Army’s Multidrug-Resistant Organism Repository and Surveillance Network (hereafter “Army”) and the above-mentioned Navy components. The nexus of the program consists of the communication and feedback loops between the Army, Navy, individual hospitals, and infection control and infectious diseases consultants to the surgeons general of the military services (arrows A–I in Figure 1). Through centralized laboratory characterization, data mining of electronic medical records, and applied laboratory research, the program provides near-real-time actionable feedback and reporting to a wide range of individual healthcare providers, committees, and agencies, to inform infection prevention policies and procedures (arrows B–H in Figure 1).

Participation and Geographic Footprint
Currently, 266 fixed medical treatment facilities are located in the contiguous United States, Alaska, Hawaii, and Germany. Most of these facilities do not regularly encounter isolates for

Figure 1. Information sharing and feedback loops used in the Department of Defense to address antimicrobial resistance. Abbreviations: AFHSC, Armed Forces Health Surveillance Center; CDC, Centers for Disease Control and Prevention; EHR, electronic healthcare record; GEIS, Global Emerging Infections Surveillance and Response System; MDRO, multidrug-resistant organism; NASS, Navy and Marine Corps Public Health EpiData Center; PII, personally identifying information.
Collection, Characterization, and Preservation of Isolates

Centralized laboratory characterization is another cornerstone of the program because it reduces outbreak-related workload of individual hospital laboratories, while ensuring the standardization and comparability of results [2–6]. Detailed methods used by the Army and Navy have been published elsewhere [7–10]. Briefly, when a targeted gram-negative bacteria, vancomycin-resistant Enterococcus spp., or methicillin-resistant Staphylococcus aureus is isolated at a DoD medical facility, it is sent to the College of American Pathologist-accredited central laboratory at the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, Maryland, that forms the hub of the program (arrow B in Figure 1). There, all organisms undergo simultaneous identification and susceptibility testing on all 3 of the major commercial analyzers (Recton Dickinson, Siemens, and bioMérieux) and pulsed-field gel electrophoresis. This testing is supplemented by manual and automated (TREK Sensititre) microbroth dilution, E-tests, and matrix assisted laser desorption ionization time-of-flight mass spectroscopy.

Selected organisms (eg, carbapenem or methicillin resistant) undergo second-generation Carba NP testing and multiplexed real-time polymerase chain reaction assays for genes encoding resistance to carbapenems (blaKPC, blaVIM, blaNDM, blaOXA, and blaSOV), mupirocin or linezolid resistance (cfr and mupA), and tolerance to chlorhexidine (qacA/B) [11–13]. Organisms of particular clinical interest, such as those from fatal infections or outbreaks or those with atypical resistance patterns, also undergo whole-genome mapping and next-generation sequencing. All organisms are archived on site, with a cryopreserved duplicate off site. A relational database, accessible through the structured query language, manages inventory and all clinical demographic, phenotypic, and genotypic information associated with each isolate.

Privacy Considerations

Army hospitals are mandated to submit isolates and personally identifiable information, to facilitate appropriate tracking and trending of results (arrows A and C in Figure 1). To safeguard privacy, all isolates are assigned a barcode immediately on receipt at the central laboratory and before processing. From that point forward, the isolates are referred to by the barcode only.

Participation by Navy, Air Force, and other agencies or organizations is voluntary. Collection of information from these isolates is not under the Army mandate, so they often arrive unidentified or without any associated personally identifiable information. This limits and slows epidemiologic analysis. All personally identifiable information is protected according to Privacy Act and Health Insurance Portability and Accountabil-ity Act (HIPAA) requirements. Before collecting information, the Army was required to complete a Privacy Impact Assessment and demonstrate compliance with the Federal Information Security Management Act and HIPAA. All data analysis and review of medical records by the Navy is done on a separate network without Internet access. Communication to infection preventionists of personally identifiable results or information is done using encryption through a secure file transfer protocol site that requires a DoD access card with a user name and password. For all purposes other than infection control feedback, deidentified labels and/or aggregated data are used.

Enhancing Compliance and Reinforcement of the Policy

To enhance isolate and data capture, the Army positions laboratory technologists at high-volume hospitals. The main role of these personnel is to submit isolates and associated data and to support that facility’s infection prevention and clinical laboratory efforts when needed. If any facility suspects a possible outbreak or breakdown in infection prevention, it can send isolates to the Army for immediate genotyping (arrow B in Figure 1). All DoD hospitals use the same centralized computer application to record laboratory results in the electronic healthcare record of the patient. This provides a unique opportunity for enhancing surveillance efforts and reinforcing submission policy.

Although the laboratory at each hospital is given instructions and single page information sheets regarding which MDR organisms (MDROs) to send to the central laboratory at the WRAIR, compliance is not 100%, even among mandated facilities. Therefore, medical informatics developed by the Navy are applied to identify and gather data from the electronic health-care record. This includes using Health Level Seven messages to collect clinical laboratory results related to MDROs (arrow D in Figure 1). Detailed methods have been published elsewhere [10]. Briefly, the Navy’s system is based on analytical and AMR tools such as WHONET and BacLink, which support algorithms for reporting drug resistance patterns, antibiogram production, and notification alerts. It uses near-real-time clinical information from confirmed laboratory results to alert laboratories, clinicians, and infection preventionists of organisms of special importance or interest, such as carbapenem- and
vancomycin-resistant phenotypes. Both the hospital and the Army are notified (arrows D and E in Figure 1). The Army is alerted to an incoming isolate of interest (arrow D), and the facility is notified and reminded to send the isolate to the Army for confirmatory testing (arrow E).

The Navy system accommodates development of profiles for emerging drug resistance patterns or new drug-resistant pathogens. The Navy can also determine, for any individual facility, how many isolates meet criteria for submission to the Army central laboratory in a given time period. This value is cross-checked against the number of isolates that the Army actually received (arrows D and E in Figure 1). If the results do not match, the individual facility is again notified to submit the isolates to the Army (arrow E in Figure 1). Compliance reports are also provided to senior military medical leadership (arrow G in Figure 1) for policy reinforcement (arrows A and I in Figure 1). The Army relies heavily on these Navy processes for comprehensive surveillance and identification of isolates of interest throughout the DoD.

Communication and Feedback

The submitting hospital is the beginning, end, and focal point for information flow in the program. After the Army characterizes the isolate, an individualized report is immediately sent to the submitting facility regarding clonality, identity confirmation, and gene content in a clinically relevant turnaround time (arrow F in Figure 1). The Navy sends reports and daily alerts that an isolate meeting criteria for submission to the Army for testing has been identified from analysis of the Health Level Seven microbiology laboratory data (arrow E in Figure 1). If the pathogen is new to the DoD or has broader implications for infection prevention, an executive summary is sent through the medical operations channels along with hospital and military health system leadership (arrow H in Figure 1).

Facility-specific and aggregated reports are regularly sent to the Quality Management Division at the US Army Medical Command (arrow G in Figure 1), which provides compliance reminders and policy reinforcement/reiteration to medical facilities and providers (arrow I in Figure 1). The Tri-Service Infection Prevention and Control Panel and the Clinical Quality Forum also receive reports to assist with their participation in the National Healthcare Safety Network of the Centers for Disease Control and Prevention (arrow H in Figure 1). In addition, regular aggregate reports are sent to nearly every infectious diseases physician, infection preventionist, and microbiologist in the DoD (not shown in Figure 1), and to senior policy makers, implementers, and enforcers (arrow H in Figure 1) who can also notify individual hospitals or all DoD facilities (arrow I in Figure 1). The Armed Forces Health Surveillance Center’s Division of Global Emerging Infections Surveillance and Response System assists with analysis of data and dissemination of reports (arrow H in Figure 1).

Cost of the Program

Based in Silver Spring, Maryland, and Portsmouth, Virginia, the program includes 20 full-time permanent employees and has a direct cost of $3.25 million annually (including reagents and consumables but excluding overheads, such as rent and utilities). At startup, an additional $2.5 million was needed for

![Table 1. Discoveries or Outcomes of the ARMoR Program](cid:2014:59 (1 August) • 393)
durable equipment and 2 years of full-time employment for 3
information technology personnel who assisted with develop-
ment, testing, and implementation of special information man-
agement infrastructure, which was not commercially available.

OUTCOMES

Since 2009, the program collected, characterized, and archived
>20 000 isolates, with the data archived in a secure, relational
database suitable for further interrogation in support of
outbreak investigations. It provided actionable feedback in a
clinically relevant turnaround time to referral centers in
major US cities and also to resource-constrained environments,
such as remote areas of Iraq, Afghanistan, and Haiti in the wake
of the 2010 earthquake [7–9, 14–18]. Theoretically, the inci-
dence of MDRO should be reduced by providing earlier oppor-
tunities for hospitals or healthcare systems to apply preventive
interventions (arrow F in Figure 1).

For this program, the discoveries and interventions have
included earlier detection of possible outbreaks or emerging

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Figure 2. Incidence rates of carbapenem-resistant Enterobacteriaceae (CRE) per 100 000 patient-years of surveillance. The bottom numbers are $P$ values for the significance of the change in relation to the base year 2005. The top number or number in parentheses above the year 2012 is the $P$ value for the significance of the change in relation to the peak year 2010. Red signifies that the change is statistically significant ($<.05$). The asterisk signifies that it remained significant after correcting for multiple comparisons.
pathogens, policy creation or modification, adjustments or intensifications of standard operating procedures, increased antimicrobial stewardship, and diagnostic assay and software development (Table 1) [7–34]. Genome sequencing and molecular characterization of pathogens for outbreak or emerging pathogen investigation were requested and subsequently provided more than 2 dozen times. These led to important discoveries and notable outcomes, especially through collaborative military-military and military-civilian partnerships (arrow J in Figure 1 and Table 1) [7–34]. Another benefit of the program is that it allows for a “2-tiered” approach. The first tier determines the baseline levels or incidences of AMR from initial surveillance. The second tier determines the effects, if any, of the interventions subsequently implemented during continued long-term surveillance on levels of AMR by continued surveillance.

Four notable examples bear mention. The first was the discovery of blaNDM1 in an unexpected species of bacteria (Acinetobacter schindleri) that eludes identification by all commercially automated analyzers [21]. This brought awareness of this problem to those in the DoD.

The second example was the ability to increase the speed and accuracy of isolate targeting, data extraction, and report generation, improving turnaround time several hundred fold through applied bioinformatics. Specifically, various factors complicate isolate targeting and data aggregation, such as the multiple definitions of MDR, extensively drug resistant (XDR), and pan-drug resistant (PDR), in addition to the different sets of susceptibility break points from agencies such as the Clinical and Laboratory Standards Institute, the US Food and Drug Administration, and the European Union Committee on Antimicrobial Susceptibility Testing.

None of the epidemiologic software packages for any of the commercially available automated identification and susceptibility testing platforms classify isolates as MDR, XDR, or PDR or employ >1 set of susceptibility break points. Furthermore, trending the change in the proportion or rates of resistant isolates over long time periods can be misleading because the observed change in proportions or rates could be due, for example, to application of a lower susceptibility break point during the surveillance period rather than to a true increase in the burden of resistance or loss of treatment options. To address these challenges, we developed an open-source, Java-based program, MDRevealer, which allows users to set their own definitions of MDR, XDR, or PDR and quickly reanalyze data and compare trends using break points from any agency or >1 set at a time. It runs on any computer processing system and is available by contacting the corresponding author [32].

The third example was the determination of the overall burden of carbapenem-resistant Enterobacteriaceae and the correlation between carbapenem and fluoroquinolone use and

<table>
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<tr>
<th>Challenge</th>
<th>Mitigation</th>
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<tr>
<td>Decreased submission of isolates to the networka</td>
<td>Conduct site assistant visits with education; offer awards for the &quot;biggest submitter&quot;; provide dedicated personnel at the laboratory of the busiest medical center, whose primary job is to submit isolates and data; provide shipping materials and pay all shipping costs</td>
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<tr>
<td>Unpredictable funding, competition for scarce funds and shrinking niches</td>
<td>Clearly articulate sustained programmatic relevance and provide instances or examples of how the program influences policy with frequent engagement of chief executive, financial officers, and information officers; diversify capabilities and deliverables, while avoiding dilution of quality and/or mission creep; collaborate with other agencies to collect data and share expertise; give agency leaders clear, concise analysis</td>
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<td>Lack of a suitable commercially available database or laboratory information system capable of handling multiple results for the same test and managing repository inventory</td>
<td>Develop a de novo customized solution using the architecture and framework of the ARMoR program's database, or use or modify the ARMoR database structure</td>
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<td>Reporting improved outcomes (eg, increased early detection or decreased infection rate) though challenging in itself, is insufficient in current fiscal climates</td>
<td>Embed data use into the agency culture; provide agency leaders with cost-benefit metrics and measures of return on investment to prove that efforts compare favorably to other programs during budget reviews; ensure that employees, stakeholders, and funding sources can easily see and analyze the data</td>
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<tr>
<td>Restricted access to state-of-the-art open-source computer programs and computer operating system software updatesb</td>
<td>Use a separately networked research enclave or .org or .edu domain</td>
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<tr>
<td>Acquisition and contracting requirementsb</td>
<td>Dedicate 1 full-time acquisition and contracting specialist for every $5 million worth of contracts and/or 20 staff members</td>
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Abbreviation: ARMoR, Antimicrobial Resistance Monitoring and Research.

a Hospital laboratories offer various reasons for not submitting isolates, including “We already knew it was resistant,” “The minimum inhibitory concentration is more important than the mechanism,” “We were unaware of the policy/mandate,” and “We were too busy and had no money to ship.”

b May not be applicable to nonmilitary or nongovernment agencies.
resistance to these antimicrobials throughout the entire DoD, through the partnership between the Army and the Navy. The report included more than 1.8 million culture results and 75 million person-years of surveillance data from all 266 hospitals. Although use and resistance was strongly correlated ($R > 0.80$) for several “drug-bug” combinations, none were significant at the national or facility level. At the regional level, however, when we combined data from the major referral centers of the southern and northern regions, inpatient consumption of fluoroquinolones was significantly associated with carbapenem resistance in *Escherichia coli* (*P < .001*) [33]. We believe that the DoD is now among the leaders of such US AMR surveillance efforts, with the first enterprise-wide report of AMR and consumption in a large, geographically diverse US population.

The final notable outcome was the decreased incidence of carbapenem-resistant Enterobacteriaceae after the program was started (Figure 2). Moreover, no further events or outbreaks involving methicillin-resistant *S. aureus* [7] or colistin-resistant *Acinetobacter* [19] have occurred at the involved facilities. Whether these outcomes were caused by or associated with the program cannot be definitively determined at this time, but no other major changes to standard operating procedures or additional infection prevention and control programs were implemented in the DoD during this observation period.

We believe that many of the processes used by the program are generalizable to other healthcare organizations, which can readily adopt the same methods, software, and assays we describe. Nongovernmental or nonmilitary organization might find fewer barriers to implementation owing to fewer inherent restrictions and institutional requirements. These, along with strategies for mitigating additional challenges such as limited funds and constricted mission space, are listed in Table 2. Through this report, we provide a framework for future implementers, solicit suggestions for ways to improve our program, and invite others to join us in collaboration.

**Notes**

Disclaimer. The views expressed herein are solely those of the authors and not to be construed as of official or representing those of the US government or the US Department of Defense.

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