COMMENTARY

Setting the Research Agenda for Preventing Infections From Multidrug-Resistant Organisms in the Veterans Health Administration

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Antimicrobials are essential to the practice of modern medicine. Prior to the discovery of these miracle drugs, physicians were helpless when faced with bacterial infections. A reminder of life before antimicrobials is a Harvard medical student's description of his slow and painful death from subacute bacterial endocarditis, which could have been treated with antimicrobials only a few short years later.[1] Over the years, antimicrobials have facilitated many medical advances by preventing and treating infections in high-risk patients, including those receiving organ transplantation and cancer chemotherapy.

Unfortunately, antimicrobial use and misuse has promoted the emergence of antimicrobial resistant bacteria, or multidrug-resistant organisms (MDROs). We are now faced with a public health crisis: the discovery of novel antimicrobial agents has slowed while the emergence and spread of MDROs has continued.[2] The very structure of modern healthcare, including the close proximity of severely ill patients treated with antimicrobials, facilitates the transmission of highly resistant pathogens. Taken to an extreme, infections due to bacteria universally resistant to antimicrobials may one day become the norm. At the present time, infections with MDROs are problematic because they require antimicrobials that are difficult to administer, more toxic to the patient, or less efficacious than other therapies.[3]

The emergence and spread of MDROs is a multifaceted problem spanning the globe and all aspects of healthcare. In the face of this public health crisis, much remains unknown. What are the best strategies for reducing the transmission of MDROs? How can antimicrobial prescribing be improved to minimize the emergence of MDROs? How can the human microbiota be manipulated to protect against colonization with MDROs? And how should these strategies be tailored across different healthcare settings and among distinct patient populations?

The response to this crisis will require comprehensive and coordinated efforts from healthcare, public health, private industy, and government. Several encouraging initiatives are already underway. For example, in 2015, the White House released a National Action Plan to Combat Antibiotic-Resistant Bacteria, which outlines specific federal activities to prevent outbreaks and the emergence of MDROs, preserve the efficacy of current antimicrobials, and foster the development of novel diagnostics and therapeutics.[4] To advance efforts to combat MDROs, the United States Congress appropriated $163 million to the Centers for Disease Control and Prevention in fiscal year 2017.[5]

The Veterans Health Administration (VHA) is well positioned to be a leader in these efforts. The VHA is the largest integrated healthcare system in the United States, with more than 1,700 sites of care and 8 million patients. The VHA reflects the spectrum of healthcare, including acute-care hospitals, long-term care facilities, and ambulatory clinics. Furthermore, the VHA has a long-standing commitment to the prevention of MDRO infections. In 2007, the VHA implemented a comprehensive program across its inpatient facilities to prevent infections from methicillin-resistant *Staphylococcus aureus* (MRSA).[6] The changes brought about by the MRSA initiative may have contributed to declines in non-MRSA infections as well.[7] National programs across the VHA have also targeted the prevention of infections from *Clostridium difficile* and carbapenem-resistant *Enterobacteriaceae*. In 2014, the VHA mandated that every facility develop an antimicrobial stewardship program. Following the VHA's lead, the Joint Commission and the Centers for Medicare and Medicaid have recently developed similar standards for antimicrobial stewardship in non-VHA facilities.

In addition to infection prevention and antimicrobial stewardship efforts, the VHA has a long history of funding

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research to study MDROs. This research has spanned the biomedical, clinical, and health services domains. While much has been accomplished both within VHA and elsewhere, there is still more to be done.

To identify gaps in our existing knowledge about MDROs and to set a research agenda for addressing these gaps, the VHA convened a group of investigators in Iowa City, Iowa, on September 14, 2016. Conference participants included experts in antimicrobial stewardship, medical anthropology, clinical medicine, epidemiology, infection prevention, pharmacy, and sociology. This meeting was made possible through the VHA Health Services Research & Development (HSR&D) service and the VHA Quality Enhancement Research Initiative (QUERI) along with support of clinical and operational partners.

The 37 participants were divided into 4 subgroups based on their areas of expertise. The rationales for these subgroups are provided below:

1. Transmission dynamics: Resistant pathogens are spread via human hands and environmental surfaces. Disrupting this transmission is essential to controlling MDROs.
2. Antimicrobial stewardship: Strategies to reduce and improve the use of antimicrobials will slow the emergence of resistant pathogens.
3. Microbiome: There may be ways to manipulate or augment the human microbiome to eradicate or prevent colonization with resistant pathogens.
4. Special populations: Strategies need to be tailored to patient populations with distinct underlying conditions and in nontraditional care settings.

One month prior to the in-person meeting, each of the 4 subgroups held a conference call to identify key points for discussion. To identify gaps in the research-to-practice pipeline, each subgroup worked through a 6-step method developed by the QUERI program.[8] Briefly, the 6-step QUERI process focuses on identifying high-risk/high-volume diseases (step 1), best practices (step 2), and variations in best practice (step 3) through epidemiologic and health service research studies. Steps 4–6 include identifying and implementing interventions to improve best practice (step 4) and ensuring that best practices improve outcomes (steps 5 and 6) through observational research, clinical trials, and implementation studies. During the in-person meeting, each subgroup discussed their preliminary findings. Subgroup decisions were made through consensus. All conclusions were shared with the remaining conference attendees for feedback and discussion.

Herein, we describe the research agenda that emerged from this conference's proceedings. Each of the 4 subgroups has prepared a summary of their findings, which are included in this current issue of *Infection Control and Hospital Epidemiology*. These summaries describe key knowledge gaps in the existing literature and important targets for future investigation. For example, the antimicrobial stewardship subgroup highlighted the need to develop stewardship strategies that work even in the absence of infectious disease specialists. Another priority is identifying which antimicrobial-prescribing metrics best predict patient- or population-level changes in antimicrobial resistance. The microbiome subgroup has argued for hospital epidemiologic studies to include longitudinal microbiota data and for future studies to assess whether fecal microbiota transplantation can eradicate MDROs from the gastrointestinal tract. In acute-care settings, there are many knowledge gaps surrounding MDRO transmission. The transmission dynamics subgroup identified multiple research targets in the following domains: hand hygiene, active surveillance, isolation measures, and environmental cleaning. Infection prevention strategies that work in acute-care settings may not be effective in populations and settings with unique patient care goals. Further research into how strategies can be tailored to these special populations is needed.

It is our hope that these proposed agendas will spur collaborative research across the VHA and throughout health care in the study of MDRO prevention. MDROs existed in nature long before humans discovered antimicrobials, and even appropriate use of antimicrobials will always promote further resistance. However, with sustained, coordinated, and aggressive efforts across the spectrum of discovery to dissemination, the current MDRO crisis may evolve into a more manageable problem.

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