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Venatorx Pharmaceuticals Highlights Two Recent Publications Indicating Rising Metallo-Beta-Lactamases for Carbapenem-Resistant Enterobacterales in US

Growing Global Incidence of Carbapenem-Resistant Enterobacterales
Metallo-beta-lactamases were the most frequently identified carbapenem resistance mechanism among Enterobacterales isolates in IHMA global surveillance

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MALVERN, Pa.--(BUSINESS WIRE)--Venatorx Pharmaceuticals, a private, pre-commercial pharmaceutical company focused on improving health outcomes for patients with difficult-to-treat drug resistant gram-negative bacterial infections and viral infections, today highlights two recent publications that provide important updates on the changing epidemiology of carbapenem-resistant Enterobacterales (CRE) globally and in the United States (US). According to a recent global surveillance publication from International Health Management Associates (IHMA), the proportion of carbapenem resistance among Enterobacterales increased from 3.3% of isolates from 2012-2017 to 5.7% in 2018-2019, a 72% increase[1]. When looking deeper at the specific contribution from carbapenemase families, metallo-beta-lactamases (MBLs) were the most frequently identified carbapenem resistance mechanism.

In the publication from IHMA[1], data from participating global hospitals in 2018-2019 demonstrated that the majority of carbapenem resistance mechanisms identified among CRE isolates collected were MBLs (36.7%). MBLs were the most frequently seen carbapenemase in isolates from Asia/Pacific (59.4%) and Africa and Middle East (49%) and were as frequently detected as *Klebsiella pneumoniae* carbapenemases (KPCs) in Europe (both at approximately 28%). In the U.S. and Canada, MBLs were found in 15.5% of all CRE isolates in 2018-2019, or approximately 1 out of every 7 CRE isolates. This represents a 300% increase from the 2012-17 period when only 5% of CRE isolates expressed MBLs in the US and Canada.[2] This frequency is also consistent with JMI Laboratories' 2021 US CRE surveillance in the US and Canada reporting 18.4% of CRE isolates carrying MBLs.[3]

In a second publication, Tamma et al.[4] of Johns Hopkins University analyzed consecutive CRE clinical isolates collected from unique patients at 3 US hospitals from 2016-2021. Of the 603 total CRE isolates, 276 expressed carbapenemases and 29 of those isolates, approximately 4.8% of all cases and 15.4% of carbapenemase-positive cases, produced MBLs.

In response to growing awareness of MBL occurrence in the US, 2023 US Infectious Diseases Society of America (IDSA) guidance [5] recommends that patients with gram-negative infections that are suspected or confirmed to contain MBLs be treated with the sub-set of CRE treatment regimens whose coverage includes both MBLs and serine beta-lactamases (SBLs).

“Since MBLs were the most frequent resistance mechanism identified globally within CRE isolates and identified in a growing proportion of US CRE isolates in the IHMA surveillance, it is essential that the next generation of antibiotics are available to combat the evolving landscape of multi-drug resistant gram-negative bacterial infections,” said Christopher J. Burns, Ph.D., Chief Executive Officer of Venatorx. “Development of new antibiotics with comprehensive MBL coverage is necessary to address global critical unmet medical needs and provide hope for patients and healthcare providers alike to effectively treat appropriate patients with these gram-negative resistant infections.”

About Gram-Negative Infections and Antimicrobial Resistance (AMR)

In a recent report on AMR, the U.S. Centers for Disease Control and Prevention (CDC) reported rates of resistance have increased significantly in the U.S. among bacterial pathogens including those commonly causing cUTI, pyelonephritis, and bacteremia. The CDC also cited that there are more than 2.8 million AMR infections annually in the U.S., which are directly related to more than 35,000 deaths.[6] Between 2014 and 2019, an analysis of U.S. UTI patients determined that 4.4% of cases were carbapenem resistant (CR) and 24.5% of U.S. UTI patients were bacteremic with 1.7% of cases caused by a CR pathogen. Patients with CR infections had a significantly longer hospital length of stay (LOS), were less likely to be discharged home, had a higher readmission rate, and had greater LOS-associated charges than patients with carbapenem-susceptible infections. Additionally, patients with bacteremia (urosepsis) due to CR pathogens had a significantly higher rate of mortality than those with carbapenem susceptible pathogens.[7]

Gram-negative bacteria have multiple AMR mechanisms that continue to adapt in response to increases in antibiotic usage. Carbapenems are broad-spectrum antibiotics that have been widely used to treat infections caused by multidrug-resistant gram-negative bacteria, including Enterobacterales. With the increased global use of carbapenems, CRE have emerged, which have limited treatment options and are associated with increased morbidity and mortality. Resistance to carbapenems among Enterobacterales is primarily achieved by production of carbapenemases, which are enzymes capable of hydrolyzing carbapenem antibiotics and most other beta-lactams and fall into two distinct families: serine beta-lactamases and metallo-beta-lactamases (MBLs). Common variants of MBLs include New Delhi MBL (NDM) and Verona Integron-encoded MBL (VIM). According to an IHMA surveillance study in 2018-2019 and JMI US Surveillance study from 2021, MBLs were the most commonly identified carbapenem resistance mechanism globally among Enterobacterales isolates, with ~16 to 18% of US CRE isolates carrying MBLs. [1,3]

While carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) is also increasing in some geographies due to emergence of MBLs, multidrug-resistant *P. aeruginosa* (MDR-PA), which may exhibit resistance to carbapenems, represents an increasing challenge for clinicians and their patients in the US and globally due to the paucity of treatment options for this primarily hospital-associated pathogen. Especially outside the US, CRPA may carry carbapenemases including MBLs (i.e., VIM); however, non-carbapenemase resistance mechanisms (i.e., efflux pumps, porins) also contribute to the growing global resistance of MDR-PA and CRPA.[8]

If AMR infections continue on this trajectory, it has been projected that an estimated 10 million people will die per year of resistant infections by 2050—a number that surpasses the projected annual number of deaths (8.2 million) caused by cancer—and the cumulative cost to the global economy could be as high as US$100 trillion.[9] In the U.S., estimates have reached as high as US$20 billion in excess direct healthcare costs, with an additional US$35 billion associated with lost productivity.[10] By 2050, the world is at risk of losing up to 3.8% of its annual gross domestic product with an annual shortfall of up to US$3.4 trillion by 2030, a figure on par with losses attributable to the 2008 global financial crisis.[11]

The Infectious Disease Society of America (IDSA) maintains updated guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections online at https://www.idsociety.org/practice-guideline/amr-guidance/.[5] For those patients who do not respond to current treatment, new antibiotic therapies are needed to combat AMR.

About Venatorx Pharmaceuticals, Inc.

Venatorx is a private, pre-commercial pharmaceutical company focused on improving health outcomes for patients with difficult-to-treat drug resistant gram-negative bacterial infections and viral infections. Venatorx’s lead asset, cefepime-taniborbactam, is an investigational antibiotic that completed a Phase 3 study (NCT03840148) in adults with complicated urinary tract infections (cUTI), including pyelonephritis. In October 2022, BARDA awarded a contract of up to $318M to Venatorx for development and procurement of cefepime-taniborbactam for the treatment of melioidosis and multidrug-

resistant infections. As part of its broader pipeline, Venatorx is also developing an oral antibacterial, ceftibuten-ledaborbactam etzadroxil, that is currently in Phase 1 clinical studies. For more information about Venatorx and its anti-infectives portfolio, please visit www.venatorx.com.

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Contacts

Media Contact
Jennifer Guinan
Sage Strategic Marketing
jennifer@sagestrat.com
610.410.8111