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White Paper

The importance of clinically relevant reference materials in antibiotic resistance research

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Antibiotic resistance is recognized as one of the greatest public health threats worldwide.[1] This concern has become significantly pronounced in the last few decades with the emergence of multidrug-resistant strains in both community- and hospital-acquired infections, resulting in extensive healthcare expenses, prolonged illness, potential disability, and death.[2] To date, there have been a number of strategies implemented with the intended goal of reducing the spread of resistance, including the discovery of innovative treatment options and the development of rapid detection methods. Despite these efforts, new resistance mechanisms continue to emerge and spread globally.[2] As such, it is imperative that newly emerging antibiotic resistance markers are identified and the corresponding strains are used as reference materials for antibiotic resistance research and development efforts. Here, we will discuss the emerging threat of antibiotic resistance; the need for novel therapeutics and rapid detection methods; and the importance of recent, clinically relevant, antibiotic-resistant reference strains in assay development and drug discovery.

Since their discovery, antibiotics have been considered miracle drugs due to their ability to safely and effectively treat infections. However, the overuse and misuse of these drugs in humans and animals have accelerated the emergence of antibiotic-resistant strains throughout the world. The spread of these strains threatens our ability to cure common infections, which can result in debilitating clinical outcomes and death.[2] Moreover, medical procedures such as cancer chemotherapy, organ transplantation, and surgery become much riskier without effective prophylactic antibiotics to reduce the risk of bacterial infection.[2,3] The detrimental effects of antibiotic resistance can already be visualized globally in the associated death toll. It is currently estimated that at least 700,000 deaths per year are attributable to antibiotic-resistant strains worldwide; this number is predicted to increase to 10 million deaths per year by 2050 if the incidence of antibiotic resistance continues to rise.[3]

Despite the need for more effective treatment options, the number of new antibiotics being produced by the pharmaceutical industry has begun to dwindle in the last several decades due to economic obstacles.[4] For the pharmaceutical industry, antibiotic development is no longer considered profitable as antibiotics are used for short-term intervals, available to consumers at low cost, and not used to treat chronic conditions.[4] Further,

when antibiotics are used, the emergence of resistance mechanisms among microbial communities is unavoidable; as such, profits can be prematurely restricted when resistance evolves.[5,6] Fortunately, the increasing awareness of antibiotic resistance has helped to spur the implementation of initiatives directed toward developing novel therapeutic treatments and improving antibiotic use and diagnostic testing.[7-9] In fact, in the span of a decade from 2005 to 2015, there have been nine new antibiotics within the tetracycline, carbapenem, glycopeptide, cephalosporin, and oxazolidinone drug classes that were approved for use, and as of March 2016, an estimated 37 new antibiotics are in clinical development.[7,10] However, historically, the success rate for infectious disease drug development is low; approximately 20% of products that enter clinical trials will be approved for patient use.[10] Therefore, it is essential that the antibiotic development pipeline is continually expanded to ensure the availability of effective therapeutics.

In addition to the production of effective therapeutic options, it is imperative to have rapid, reliable, and accurate methods for identifying antibiotic-resistant infections. Because multidrug-resistant infections are difficult to treat, the timely detection of these strains and the identification of effective therapies are essential. Currently, there are a variety of culture- and molecular-based approaches available for the detection and identification of multidrug-resistant strains. Culture-based approaches are phenotypic tests that involve growth inhibition assays performed in broth or by agar disc diffusion.[11,12] Though these assays are easy to perform, they can be quite laborious and time intensive, particularly if the infecting strain is fastidious or has a slow growth rate. Further, not all microbial species are culturable outside of their host environment.[11] In contrast, newer molecular-based methods of detection, such as polymerase chain reaction (PCR), quantitative PCR (qPCR), and microarrays, enable faster turnaround times, are considerably more sensitive and specific, and can be optimized for use with direct clinical samples.

More recently, next-generation sequencing and metagenomics have become important tools for the identification of antibiotic resistance genes as well as understanding how these genes are acquired over time, making them useful for surveillance and clinical management decisions.[11,13] Though molecular-based technologies provide a number of benefits, they still require the availability of appropriate instrument platforms, which may be cost prohibitive or require technical expertise.[14] These issues created an even higher barrier for use in the developing world. Further, sequencing-based technologies require data analysis management and access to databases with known sequence information[15]. Overall, there are a number of different technologies and methods that can be implemented or developed for the detection of antibiotic resistance, each having its own list of potential benefits and pitfalls.

When generating or implementing tools for the detection or treatment of multidrug-resistant infections, authenticated reference materials are essential for use as controls. For example, for the development of novel therapeutic methods, clinically relevant microbial strains with known antibiotic susceptibility profiles are ideal for evaluating the efficacy of novel therapeutics against different antibiotic-resistant pathogens. These reference materials would also be effective in evaluating the sensitivity and specificity of existing or novel detection methods during implementation or development. In both cases, the use of fully authenticated and characterized reference materials are necessary as the reliability of these strains impacts the quality and efficacy of therapeutic treatment and detection methods, which in turn affects the health and recovery of patients.

To support the need for reliable reference materials for antibiotic resistance research, ATCC has created a comprehensive assortment of antibiotic-resistant strains, collectively known as the Global Priority Superbugs collection. This assembly of clinically relevant and extensively characterized antibiotic-resistant isolates provides access to newly emerging resistance markers and priority pathogens that are critical for research and development. Moreover, these strains have validated phenotypic activity against a variety of drug classes and are provided with minimum inhibitory concentrations and susceptibility profiles for targeted drugs, DNA sequence information for antibiotic resistance genes and 16S rRNA genes, and expanded levels of source metadata. Thus, these products are essential tools for the discovery of novel therapeutics and the development and implementation of new detection assays.

Overall, antibiotic resistance is a serious, globally extensive problem that significantly affects patient morbidity and mortality. To help reduce the emergence, transmission, and effects of antibiotic-resistant pathogens, the development and implementation of novel therapeutic treatments and detection methods are of the utmost importance. To support this endeavor, ATCC offers an expanding collection of clinically relevant, antibiotic-resistant strains that are provided with extensive levels of source metadata and genotypic and phenotypic characterization for use as reference materials in drug discovery and development as well as assay design and application.

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