L.E.K.

EXECUTIVE INSIGHTS

VOLUME XVII, ISSUE 38

Diagnostics for Superbugs: A Lynchpin for Turning the Tables on this Global Scourge

The most recent estimates suggest that approximately 700,000 deaths are caused globally each year by antimicrobial-resistant microorganisms. The Organization for Economic Co-operation and Development (OECD) estimates that current rates of antibiotic resistance will also result in cumulative economic costs of approximately $3 trillion by 2050.[1] Furthermore, the situation is getting worse: Antibiotic resistance is increasing at an alarming rate, with some highly virulent pathogens (e.g., CRE) quickly evolving past the point of treatment with current drugs. Unfortunately, antibiotic development, especially for more dangerous Gram-negative infections, has declined over the past 30 years[2] and remains weak and underfunded due in large part to these products' low economic return.

The Key to Unlocking the Paradox

While several interrelated barriers contribute to low returns on antibiotics, the two biggest issues are that novel, more targeted antibiotics:

- Are constrained to late-line therapy, after one to three courses of broad-spectrum antibiotics
- Have little pricing power relative to their clinical impact and other drug classes

A lack of effective, rapid precision diagnostics (Dx) to target antibiotic use more effectively is a critical exacerbating factor behind these barriers.

Without rapid, precision Dx to target therapy, physicians generally treat empirically, prescribing widely available and inexpensive broad-spectrum antibiotics. Empiric use of broad-spectrum agents can lead to poor patient outcomes and also contributes to growing antibiotic resistance. Only after broad-spectrum antibiotics fail or susceptibility data comes back from the lab (which can take two to four days) do physicians generally consider novel/targeted antibiotics.

The diagnosis-related group (DRG)-based reimbursement system in most of Europe and the U.S. generally incentivizes hospitals to use the least expensive therapy possible to treat patients effectively. Because cheap, generic, broad-spectrum antibiotics are widely available, this system exerts strong pricing and utilization pressure on branded antibiotics, creating strong economic disincentives for pharma companies to develop novel targeted antibiotics given relatively poor returns vs. other disease areas.

While we expect pricing dynamics to improve over time (for more information about this topic, see our *Executive Insights* titled: "The Paradox of Antibiotic Pricing"), hospitals and

Diagnostics for Superbugs: A Lynchpin for Turning the Tables on this Global Scourge was written by **Jonathan Kfoury** and **Alex Vadas**, managing directors, and **T.J. Bilodeau**, U.S. practice manager in L.E.K. Consulting's Biopharma and Life Sciences practice. Jonathan is based in San Francisco, Alex is based in Los Angeles and T.J. is based in Boston. For more information, contact lifesciences@lek.com.

national/private payers are unlikely to pay for more expensive targeted antibiotics without confirmation from rapid Dx solutions that targeted products would be more effective than cheaper broad-spectrum options.

Therapies in other areas of high unmet need, such as oncology and rare disease, have achieved remarkable pricing power because, in part, they are highly targeted and use Dx to provide confidence that their high cost is justified to treat certain patient segments.

As a result, rapid precision Dx and decision support infrastructure will be critical to changing the treatment paradigm and unlocking the economic potential of novel targeted antibiotics. Better guidance from rapid Dx will not only encourage earlier use of targeted antibiotics, where appropriate, but it will also provide greater confidence in their value, which should translate into more pricing power. Most importantly, rapid precision Dx will help improve both patient and public health outcomes by reducing overuse of broad-spectrum agents, which results in greater morbidity/mortality and resistance development, as well as increased overall healthcare cost.

A Multi-pronged Challenge

There are several challenges that have limited the use of diagnostic testing to drive early-line treatment decisions for serious bacterial infections, most notably:

- Inadequate turnaround time
- Inability to accurately identify the causal pathogen and its susceptibility profile
- Laboratory workflow challenges
- Cost/reimbursement issues

While culture-based methods are the gold standard in effectively identifying the causal pathogen and testing its susceptibility to antimicrobial agents, these methods take two to four days, forcing physicians to treat patients empirically until definitive test results arrive. In the context of a fast-moving, life-threatening bacterial infection, physicians need a solution that enables them to make informed clinical decisions in hours, not days.

The introduction of new Dx tests gives rise to reimbursement-related challenges. Securing a new reimbursement code is both complex and time-consuming, and reimbursement often does not reflect a test's clinical value, factors which constrain test manufacturer interest. In addition, health systems often require objective studies that establish effectiveness both clinically and in terms of cost before they will fully adopt a new Dx technology. These trials can be prohibitively expensive for a diagnostic company to fund on its own given uncertain reimbursement rates upon commercialization.

In addition, while several newly launched technologies have made significant progress on more rapid detection of pathogens and susceptibility, many of these solutions, including molecular Dx tests and syndromic panels, still have limitations related not only to turnaround time but also to cost and test performance (see Figure 1). For instance, although molecular Dx tests can identify a causal pathogen in under 60 minutes, these tests currently are available only for a limited set of pathogens, have high rates of false positives, and susceptibility tests typically must be run separately.

New Reasons for Hope

Although the situation appears bleak, a confluence of emerging factors is likely to buoy increased development and use of rapid Dx tests and targeted antibiotics moving forward in order to achieve better patient care.

Numerous governments have created new initiatives and policies over recent years, such as the U.K.'s Review on Antimicrobial Resistance, OECD/G7 report on Antimicrobial Resistance, the GAIN Act and more recent PCAST report in the U.S.,[3] and associated multi-billion-dollar funding programs[4]

Figure 1
Comparison of Various Pathogen Detection Technologies

	Technology	Example Vendors	Time to Result	Cost per Test	Pathogen Detection Capability		
					Broad Coverage	Direct from Whole Blood	Antibiotic Susceptibility
Established	Traditional Culture + AST	Becton Dickinson, bioMerieux	2–3 days	<$10	Yes	No (requires positive culture)	Yes (phenotypic measurement)
Established	qPCR (Includes Point of Care)	Cepheid, Alere, Roche	<90 minutes	$20 – $50	Limited to few targets	No	Yes (inferred from genetics)
Established	Multiplexed qPCR	BioFire, Nanosphere	1 – 2 hours	>$100	Yes (multiplexed)	No	Yes (inferred from genetics)
Emerging	MALDI-TOF	bioMerieux, Bruker	<1 hour	Negligible (instruments cost >$200K)	Yes	No	Potentially (unproven)
Emerging	NGS	Illumina, ThermoFisher	1–2 days	>$100	Yes (hypothesis free)	Potentially (unproven)	Yes (inferred from genetics)
Emerging	Direct Detection	Roche (GeneWEAVE)	<4 hours	Not disclosed	Yes	Yes	Yes (phenotypic measurement)
Emerging	Direct Detection	T2 Biosystems	3–5 hours	$175 – $250	Yes (multiplexed)	Yes	Potentially (inferred from genetics)
Emerging	Direct Detection	Abbott (Iridica)	~6 hours	Not disclosed	Yes (broad coverage)	Yes	Yes (inferred from genetics)

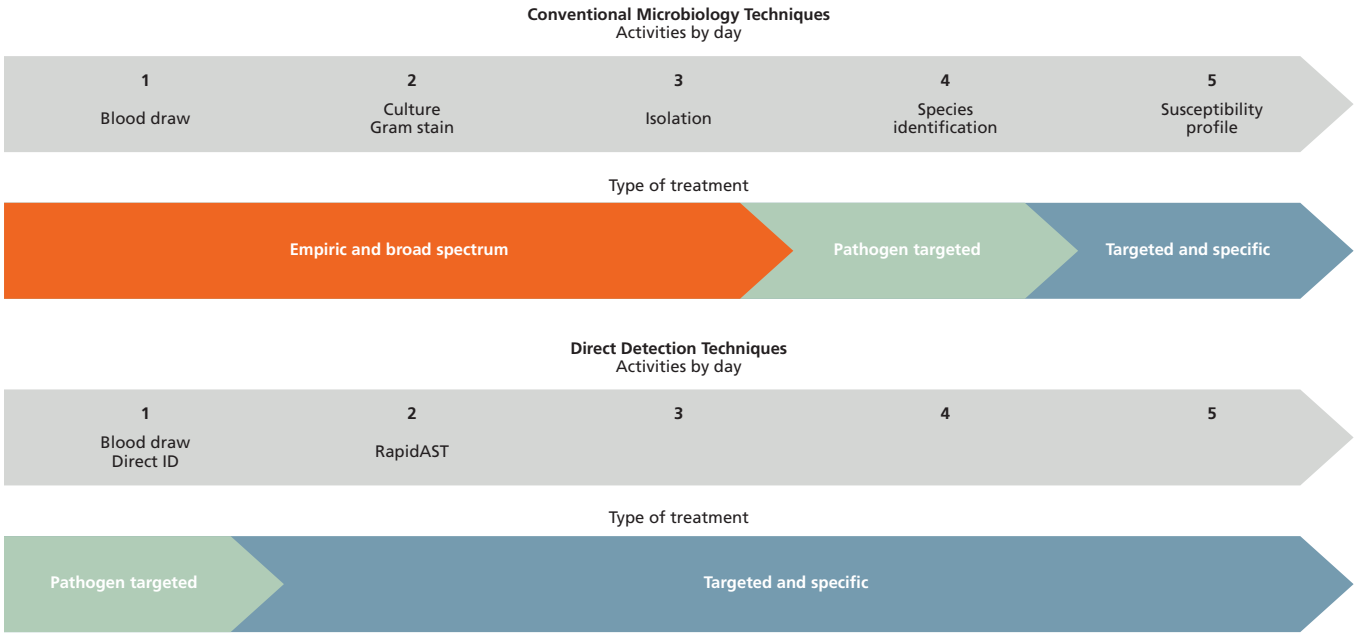
aimed at incentivizing the development of targeted antibiotics and rapid Dx to address the growing danger from antibiotic-resistant infections. These new policies, along with the willingness of governments, payers and hospitals to discuss changes to development pathways and reimbursement levels, have spurred renewed interest in antibiotics from the pharma community.

Meanwhile, emerging Dx technologies and artificial intelligence-based decision support solutions on the horizon could help physicians determine the most appropriate antibiotic for each patient in a clinically meaningful timeframe. Next generation MALDI-TOF[5] technology with rapid AST capability and other rapid phenotypic or direct detection tests, such as the GeneWEAVE vivoDx, could change the treatment paradigm (see Figure 2). These new technologies appear to have many or all of the essential characteristics for success:

1. The ability to accurately identify both the causal pathogen and determine its susceptibility
2. Quick turnaround time
3. Simple operation across several sample types without the need for a positive culture

In addition, artificial intelligence (AI) systems, such as IBM Watson, are effectively being taught to provide diagnostic information and treatment recommendations to cancer specialists, a development that if applied to infectious disease could bolster physicians' ability to make faster and more accurate clinical decisions. Although these technologies are still in development, solutions that enable physicians to determine the most appropriate targeted antibiotic in a clinically meaningful time frame appear to be on the horizon. Using accurate, cost-effective, rapid Dx in tandem with an informatics or AI-driven decision support infrastructure is critical to helping address the growing public health threat and the substantial economic costs driven by antibiotic resistance.

Figure 2
Impact of Emerging Dx Techniques on Antibiotic Treatment Paradigm



Source: L.E.K. analysis, *Journal of Clinical Microbiology*, Pathological Society of Great Britain and Ireland, Illinois Society for Microbiology

The key trend in healthcare towards increasingly evidence-based, cost-effective and outcomes-driven care only bolsters this technical progress. As economic incentives shift to favor a focus on patient outcomes and cost-effective, value-based care, national payers and hospital systems are taking a more holistic view of the impact that antibiotic resistance has on both cost and outcomes. As a result, these groups are becoming more receptive to addressing some of the issues surrounding reimbursement and clinical guidelines, which previously created barriers to the clinical and commercial successes of targeted antibiotics and rapid Dx.

The Path Forward

Unfortunately, the efforts of a single stakeholder group or government will not be sufficient to drive the effective development of rapid precision Dx and a decision support infrastructure that helps address this dire threat from superbugs. In view of the inter-connectedness of the core challenges around development and use of rapid, precision diagnostics, it will be key for expanded partnerships between diagnostic, pharma and technology/informatics companies, as well as key stakeholders such as governments, regulatory bodies and hospital systems, to support successful development and commercialization of this more targeted paradigm.

In light of these dynamics, we recommend the following:

1. Creation of public/private consortiums of pharma, diagnostics and governmental organizations, by expanding existing partnerships such as TATFAR[6] across developed pharma markets (initially between the EU and U.S.) with a focus on sharing information, funding development and accelerating innovation in rapid precision Dx — with supporting informatics/decision support infrastructure

2. Greater focus by biopharma on proactively incorporating emerging Dx technologies into the early/mid-stage development of targeted antibiotics, especially for resistant pathogens with well-identified unmet needs[7]

3. Establishment of health economics and outcomes research (HEOR) pilots with integrated delivery networks and/or governmental organizations, such as the CDC or OECD, to demonstrate the economic and patient-outcomes value of both targeted antibiotics and rapid Dx/decision support solutions

Implementing these recommendations will help improve global coordination of key stakeholder groups and focus their efforts on the activities most likely to move the needle. Together these efforts should help turn the tables on antibiotic resistance over time, sharply improving both patient and public health outcomes, and bending down the spiraling global cost-curve associated with antimicrobial resistance.

[1]OECD estimates that hospitals spend, on average, an additional $10,000 to $40,000 to treat a patient infected by a resistant pathogen. This means that compared to a world without AMR, OECD countries may experience cumulative losses of $2.9 trillion by 2050.

[2]1983 – 1992: 30 antibiotic approvals; 1993 – 2002: 17 antibiotic approvals, 2003 – 2012: 8 antibiotic approvals.

[3]Generating Antibiotics Incentives Now (GAIN) Act expedited the regulatory process and lengthened market exclusivity for qualified infectious disease products in the U.S.

[4]President Obama advocated for a $1.2 billion increase in federal funding for combatting and preventing antibiotic resistance. The commission for The Review on Microbial Resistance, chaired by economist Jim O'Neill, recommended a $2 billion global fund for antibiotic research.

[5]Matrix-Assisted Laser Desorption/Ionization Time-of-Flight mass spectrometry.

[6]Transatlantic Taskforce on Antimicrobial Resistance.

[7]The CDC has classified eight pathogens as "urgent" or "serious" concerns: CRE, MDR N. gonorrhoeae, MDR Acinetobacter, VRE, MDR P. aeruginosa, nontyphoidal Salmonella, MDR nontyphoidal Salmonella, MDR S. pneumoniae, and MDR tuberculosis.