Inappropriately prescribed antibacterials for viral respiratory illness contribute to increased healthcare costs, unnecessary drug-related adverse effects, and drive antimicrobial resistance. The inability to rapidly and reliably distinguish bacterial from viral or non-infectious etiologies is a major impediment to appropriate antibiotic use. Pathogen detection strategies can be helpful but are limited by poor sensitivity, long time-to-result, inability to distinguish infection from colonization, or restricted number of target pathogens. Peptide biomarkers such as procalcitonin may also be helpful but are poorly sensitive and specific. Consequently, these approaches have not adequately addressed the antibacterial overuse problem. We therefore propose an innovative solution focusing on the patient’s response to infection. New scientific advances can now capture the entirety of the host response using system-wide molecular surveys (e.g., RNA, proteins, metabolites). We have developed analytical methods to define the stereotyped responses found within these highly complex and dense data. Applying these techniques to infection, we have shown the pattern of immune system response can distinguish bacterial, viral, and non-infectious etiologies. That response is most robustly detected in the patient’s gene expression profile, which is far more accurate than existing diagnostic tests. This strategy is only useful, however, if it can be measured rapidly, simply, and at the point-of-need. Supported by the Antibacterial Resistance Leadership Group, Duke University and BioFire Diagnostics now propose such a test. This simple-to-use, 1-hour test distinguishes bacterial infection, viral infection, or neither so as to guide the appropriate administration of antibacterials at the point-of-need.