Stuart Levy

Seeking to maintain a supply of effective antibiotics, Stuart Levy combines research in microbiology and antibiotic drug discovery with a strong commitment to public communication.

"Thirty years ago, I began talking out about the inappropriate use of antibiotics for growth promotion in animal husbandry." From this beginning, Stuart Levy has been an outspoken advocate for the prudent use of antibiotics. Although doctors have certainly become more cautious in prescribing antibiotics, the US meat industry continues to use them (this has now been banned in Europe), and consumer products increasingly contain antibacterial agents. More ominous is the fact that there has been remarkably little progress in the development of new antibiotics and a disturbingly high increase in the incidence of multi-drug-resistant bacteria.

As a professor of molecular biology and microbiology and of medicine at Tufts University School of Medicine, and as director of the Center for Adaptation Genetics and Drug Resistance, Stuart Levy directs research on mechanisms of bacterial antibiotic resistance. He also serves as the president of The Alliance for the Prudent Use of Antibiotics (http://www.tufts.edu/med/apua/), a global organization directed at promoting the appropriate use of antibiotics and reducing antibiotic resistance worldwide. He participates more directly in antibacterial discovery efforts as the chief scientific officer for the biotechnology company Paratek Pharmaceuticals (http://www.paratekpharm.com/).

Although hospitals have long been a primary location of multi-drug-resistant bacterial infections, Levy describes how in the last few years, "there are now bacterial infections being transmitted in the community that are multi-drug resistant and potential killers." There is a community-acquired strain of *Staphylococcus aureus* that, as Levy describes, was "originally only resistant to the penicillins and cephalosporins, but it has picked up plasmids which give it resistance to erythromycin, clindamycin and tetracycline, and it has emerged with chromosomal resistance to quinolines." Another community-acquired bacterial strain, *Mycobacterium tuberculosis*, has now been dubbed 'XDR' for extensively drug resistant. This acquisition of multi-drug resistance is disturbingly predictable, according to Levy. "Bacteria enter a new community and what do they do? They just pick up one resistance from one bacteria and another from another bacteria." As a result, strains are created that are difficult or impossible to treat.

In addition to the rise of resistance in the community, there is still cause for tremendous concern about multi-drug resistance in hospitals. "The biggest problems have always been in the hospitals," says Levy, "because they are the sickest patients and because so much antibiotic use occurs in hospitals." With the recent identification of vancomycin-resistant staphylococci and enterococci, there was the fear that some Gram-positive bacterial infections would become untreatable. Since that time a few new drugs (daptomycin, linezolid and dalfopristin/quinupristin) have been developed that are effective against vancomycin-resistant bacterial infections. So, in this case there are now options. However for some of the Gram-negative bacterial infections—*Acinetobactor baumanii*, *Pseudomonas aeruginosa*, broad-spectrum-resistant *Escherichia coli* and *Klebsiella pneumoniae*—"we don't have new drugs and there's nothing really that I see in the pipeline," Levy warns. It is for these Gram-negative bacteria that there is the greatest need for new antibiotics.

The question is how to target these highly drug-resistant Gram-negative bacteria. Levy is involved in developing new antibiotics as cofounder and chief scientific officer of Paratek Pharmaceuticals. They are working on new tetracycline derivatives, which are effective against resistant *E. coli* and *K. pneumoniae*, but not against some of the most resistant infections such as *P. aeruginosa* and *A. baumanii*. For these cases, Paratek is working on an antibiotic that would inhibit a global virulence transcriptional regulator. By targeting a virulence factor, they believe that the antibiotic could be used to prevent infections in individuals at high risk. Because the antibiotic does not kill the bacteria, there is also the hope that there would be less selective pressure for the development of resistance. Levy sees that more scientists are now thinking, "maybe we should look at antivirulence and not death as a new goal in controlling infectious diseases."

Despite an obvious need for more effective antibiotics, an important practical question is how to encourage research and development of the next generation of antibiotics. Levy feels that "we need a steady group of companies that make antibiotics for the world." How do you get companies to contribute? To make antibiotic development financially attractive, Levy feels that governmental incentives are necessary. For instance, the incentive to the company could be "if you find an antibiotic, we will extend the patent life or we may let you pick a drug in your portfolio and extend its patent life." Companies can also be encouraged to help contain resistance that occurs in a hospital in which a drug is being wrongly used, which can extend the usefulness of the drug. Levy feels that new incentives are critical because otherwise "the numbers of companies are drying up."

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Aside from the need for effective antibiotics, an additional challenge in treating these infections is that if you don't start out with the right drug, then the infection can be rapidly fatal. "That's been the abyss of our therapeutic challenge," according to Levy. "We don't have a rapid diagnostic to tell us if it is going to be susceptible, so we give it all the guns, which then selects for all the resistances." Rapid diagnostics are needed for identifying the bacterial cause of the infection and its susceptibilities. Levy would like to see a situation in which a person "comes in with an infection, a sample gets sent to the lab, and 20 minutes later they call back and say, 'This is a staph infection, and it's susceptible to methicillin.'"

Alongside his research program in microbiology, Stuart Levy began speaking to the public about antibiotic resistance more than 30 years ago. He describes how he "went on Good Morning America as a young investigator sitting on a tall chair being interviewed by Bryant Gumbel, and it was not comfortable." From this tentative beginning, he has embraced communicating with the public as an essential complement to his scientific career. Given the increasing importance of public understanding of complex scientific issues, Levy provides a model for the active involvement of scientists in conveying accurate information.

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