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New antibiotic agents in the pipeline and how they can help overcome microbial resistance

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Bacterial resistance is a growing threat and yet few new antibiotics active against multi-resistant bacteria are being explored. A combination of falling profits, regulatory mechanisms and irrational and injudicious use of antibiotics has led to an alarming situation where some infections have no cure. In this article, we summarize the new developments that have been suggested to incentivize the pharmaceutical industries toward the field of infections. We also briefly mention the new compounds on the horizon and some newly approved compounds that might help us tide over this crisis.

Introduction

Antibiotics are unique among all medicinal formulations used in therapeutics. They are the only class of medicinal agents whose primary target is not the human tissue or its products. Rather, antibiotics act on bacteria and this has dramatic downstream consequences. Antibiotics disturb the natural ecological harmony by way of exerting an evolutionary pressure on bacteria. Antibiotics have revolutionized human development in a way that few other scientific discoveries have. They have not only enabled us to overcome the "captain of the men of death" by saving lives of patients with serious infections, they have played a pivotal role in major advances in medicine and surgery (not just infections), a role which is less often highlighted and yet has paramount significance. Major complicated surgical procedures, transplants, advances in neonatal medicine, and advances in chemotherapy for cancer patients would not have taken place without antibiotics.[1] Other than vaccines, few medical discoveries have had such a wide ranging impact on healthcare delivery. And yet we have reached a stage today where serious threats are being posed by drug-resistant bacteria. This threat was always on the horizon. As early as 1943, Sir Alexander Fleming noted that the microbes are educated to resist penicillin but over the last several decades very little has been done to combat the emerging threat of drug resistance.[2] Measures such as antibiotic stewardship and infection control have been applied but these measures have been taken locally and sporadically often as a reactionary tool rather than as part of any strategic planning and vision.[3] In any case, these measures have only provided temporary benefit. The scientific advancements in terms of discovery of new molecules and targets have suffered from even more lethargy and also from lack of direction. There are very few agents in the pipeline relative to the situation in the 1970s but more alarmingly, even in absolute terms. In this review we first look at the problems that we face today along with possible solutions. We then briefly discuss what is new with guarded optimism.

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The Era of Stunted Growth

In order to address the lack of growth in the field of new antibiotics, we must first understand the reasons for the stunted development in this area.

The nature of antibiotic use. Compared with other drugs (e.g., agents for diabetes, hypertension and cholesterol-lowering agents), antibiotics are typically used for short courses (5–7 d) other than for specific illnesses such as bacterial endocarditis. Thus, the total consumption of antibiotics, although sufficient to generate resistance in bacteria, is not enough from the point of view of commercial viability.[4]

Suboptimal approach. Second, the threat of emerging resistance has led to some behavioral changes in prescribing practices but the impact has been suboptimal. Not enough has been done by way of legislation to curb inappropriate prescribing but at the same time the half-hearted self-regulatory approach has had an adverse impact on the use of newer agents (some more potent and some non-inferior to established generic medicines) such that new antibiotics are now used as last line drugs to combat serious illnesses often for right reasons (e.g., cost of treatment). When new agents do get used eventually, emergence of resistance at some point is almost inevitable.

Unbalanced development. The Antimicrobial Availability Task Force of the Infectious Diseases Society of America (IDSA) in its report found significant variability in development of new antibiotics.[5] For example, pharmaceutical companies appeared to take a more active interest in developing antibiotics for methicillin-resistant *Staphylococcus aureus* (MRSA) compared with Gram-negative pathogens such as *A. baumannii,* ESBL-producing *E. coli* and Klebsiella and *P. aeruginosa*. The most likely explanation for the imbalance is the market. While MRSA has been recognized as a major problem in hospitals in the developed countries, the market for treating Gram-negative organisms is smaller and somewhat unpredictable given the rapidity of acquisition of

resistance. However, the threat of full blown emergent resistance in Gram-negative bacteria is no less menacing and the problem can no longer be ignored for reasons such as geographical isolation. The detection of the New Delhi metalloenzyme (NDM) β-lactamase carrying bacteria in the UK from patients with a history of travel to Asia is well documented.[6] The bacteria carrying the gene that encodes for the NDM are susceptible only to colistin and sometimes, tigecycline. In addition, the rapid emergence of *Klebsiella pneumoniae* carbapenemase (KPC) producing bacteria has led to significant problems worldwide because optimal treatment options are unknown. Data suggest that carbapenem resistance was rare before 2001 but since then outbreaks of KPC producing strains have been reported. KPC producing strains are susceptible only to colistin and tigecycline.[7-10]

Uncertain future. Third, the uncertainty of bacterial evolution means that resistance is not predictable. Manufacturers who invest large sums of money into projects involving antibiotic development may find that there are not enough returns as resistance to the new antibiotics stifles the successful marketing of the product. If they do manage to successfully launch a product, there are other barriers to surmount. The economic uncertainty of the last few years has had a restraining effect on the end-users. Developed countries with funded healthcare are applying austerity measures while developing countries such as China and India still have a large cohort of population that still cannot afford expensive new medicines.

Over-regulation. Finally, existing regulatory and approval pathways have also been responsible for stifling progress on new antibiotics.[1] These regulations have been criticized for using unbalanced risk-benefit equations. For example, multidrug-resistant bacterial infections are unlikely to be tested in large clinical trials because of limited number of patients but nonetheless, the threat of emerging and widespread resistance should be a sufficient trigger to prepare in advance. The rigid nature of the approval process has paradoxically led to a reduction in the availability of new antibiotics while resistance to the currently used agents continues to grow. Between 1983 and 2007, a substantial reduction in the number of new antibiotic approvals was demonstrated.[11] Shlaes and Moellering have discussed how alterations in the requirements for trial designs can have significant impact on the size of the trial and hence cost of conducting trials. They describe how a change from a 15% δ design to a 10% δ design would increase the cost of the trial by more than 100%, something which only the biggest pharmaceutical companies can afford but even they would in all likelihood deprioritize areas of research where the cost could be recovered but only with difficulty.[12]

Steps to Revitalize the Industry

Manufacturers for whom the commercial interests and accountability to shareholders are of paramount importance thus prefer to invest safe in medicines for chronic conditions rather than the medicines that actually lead to a rapid cure. The greatest challenge that confronts us today is to get the right balance so as to incentivize the pharmaceutical companies toward developing antimicrobial agents. The Infectious Diseases Society of America has recently proposed a limited population antibacterial drug (LPAD) approval pathway that would facilitate smaller and less expensive trials.[13] Such limited approvals (e.g., orphan drug programs) already exist in other situations where the disease in question is one that is rare.

There have been some other encouraging steps of late. The LPAD proposal discussed above complements the Generating Antibiotic Incentives Now (GAIN) act and the Strategies to Address Antimicrobial Resistance (STAAR) Act, both of which are before the US Congress.[1] These legislative acts attempt to address some of the wider issues that impact on the pharmaceutical industry. The IDSA has also recently published its recommendations in order to address the concerns surrounding antibiotic resistance. On one hand, it is vital to combat the rise in resistance and on the other hand, it is imperative that steps be taken to favor resurgence of new antibiotics. While logic dictates that interest in antibiotic development should be fuelled by emerging resistance, in reality the opposite has happened perhaps related to the fact that approval of new antibiotics has slowed resulting in a withdrawal response from major pharmaceutical companies. Some of the suggested measures include:

Economic stimulus. Economic incentives should be provided by way of promoting public-private partnerships and government-supported collaborative programs. In the US, it has been proposed that a special fund be created by levying an Antimicrobial Innovation and Conservation fee on the dispenser when a wholesale purchase is made. A part of this sum should then be allocated to antibiotic stewardship fund and the remaining be transferred to a trust fund to support the development of new antibiotics.[1] A recent venture in Europe is currently supported by a €224 million research grant to facilitate the development of new antibiotics. Known as the Innovative Medicines Initiative, this joint venture between the European Union and the European Federation of Pharmaceutical Industries and Associations aims to utilize a significant proportion of the funding by 2020.[14]

Regulatory approaches. As discussed above, the regulatory mechanism has been unable to keep pace with the growing threat of resistance and as a result interest from researchers and the industry has declined over time. The "over-conservative" approach related to the size of antibiotic-related drug trials and the setting up of non-inferiority margins has met with criticism from several quarters. Thus new regulatory approaches are needed to ensure that both safety as well as clinical utility be considered in the decision making process. At the same time, a microbe-driven clinical study as opposed to a disease-driven study may facilitate clinical trials whereby all infections caused by a resistant pathogen are studied under a "pathogen umbrella" (e.g., multidrug-resistant Acinetobacter infections) rather than a "clinical umbrella" (e.g., community-acquired pneumonia) which may lead to eventual inappropriate usage (e.g., for less resistant pathogens) if at all it provides sufficient numbers for the trial to take place. Thus, the current approach to the design itself needs to be scrutinized.[1] A novel approach suggested is a two-step conditional approval process whereby limited license may be provided for a defined indication followed by additional

approvals based on further clinical data and research.[15] On the other hand, adequate safeguards need to be put in place so that harm is avoided.[16]

Antibiotic vigilance. An inevitable outcome of antibiotic use is development of resistance unless measures are taken to curb inappropriate prescribing. Efficient surveillance systems are required so that any trend in growing resistance is noticed early. At the same time, antimicrobial stewardship needs to be promoted at every level by supporting the program in hospitals as well as community. Guidelines for promoting antibiotic stewardship are widely available but management support would be necessary in order to facilitate this process in hospitals.[17] Increasingly, antibiotic stewardship is being seen as an issue of national importance. In 2008, the California Department of Public Health was required to develop a process for judicious antibiotic use as well as to monitor the process by way of legislation (The California Senate Bill 739). It has been reported that almost a quarter of hospitals were influenced by this legislation leading to the establishment of an antimicrobial stewardship program. A recent guidance from Society for Healthcare Epidemiology of America proposes to broaden the scope of this legislation.[18]

Investing in research. Research into antibiotics should be a priority at every level: basic molecular biology to identify targets, pharmacological research to optimize drug delivery and clinical research to identify the patient population likely to benefit most. Unfortunately, technology to detect multidrug-resistant organisms early is still not available. The ability to detect infection with multi-resistant organisms is crucial in order to generate sufficient number of patients for the purpose of clinical studies if trials selectively for patients infected with multi-resistant pathogens are to be performed.

Collaborative development. One other area that deserves mention is the scope of scientific collaboration between major drug companies. Such collaborations might potentially decrease wasteful competition. However, the practical difficulties in such projects are enormous. Public-private partnerships also provide stimulus for investment. The Wellcome trust grant to GlaxoSmithKline for research in antibiotics with activity against Gram-negative bacteria is an example of a successful collaboration.[19]

The Story of Penicillin: Can We Learn Any Lessons for Today's Needs?

It is worth revisiting the history of penicillin, originally discovered by Alexander Fleming, a noted academic microbiologist working at St. Mary's University Hospital, London, in 1928. Fleming realized some of penicillin's possibilities but was thwarted by lack of access to expert chemical knowledge. Even when the substance was picked up by Florey and Chain, at that time working in Oxford, after the three of them were at an International Microbiology Conference in the US on the eve of the Second World War, development was not easy. In reality, it took the combined efforts of several large international pharmaceutical firms, working in tandem with the US and UK governments to bring the project to fruition.[20] This highlights just how difficult it was, and no doubt remains, to discover and develop new agents. Collaboration between companies and waiving of patents was probably easier then, because of the war and pressure from government. Moreover, today's complex regulatory environment did not exist, with the need for prolonged and expensive clinical trials. While academia clearly played a valuable role in the penicillin history, and no doubt can again discover valuable new agents, history shows that most antibiotics were discovered by large scale commercial screening programs, and industry is essential for the successful development of virtually all antibiotics.

How Would New Antibiotics Impact Favorably on Drug Resistance?

While the aforementioned "antibiotic doomsday" scenario is not unreal, a few agents in the pipeline do provide a sense of optimism. It is important to highlight here that the thrust over the past two decades has been to develop congeners of existing potent antibiotics in a given class. Such a strategy offers a safety margin to the manufacturers because the class of drug is already known to be active. On the other hand, finding a novel target, possibly with no cross resistance, has elements of uncertainty but successful outcomes may translate into significant profits. The approach one chooses depends upon a number of factors. These include internal factors such as stability within pharmaceutical industry and vision at the executive level and external factors such as the relationship between industry, regulators and health care providers and also factors such as economic situation of the time and accuracy of projections for economic growth in the future.

Nonetheless, the agents that are discussed below may offer a brief respite in the short-term and in the worst case scenario, they may buy some time that allows the policy makers and the industry to react to the growing threat of resistance. Development and availability of new antibiotics would prevent any undermining of our ability to treat serious infection in individual patients, boost confidence in meeting with threats such as bioterrorism, and might even have a favorable impact on development of antibiotic resistance in the future by the practice of novel strategies such as antibiotic cycling and mixing for which some evidence exists.[21]

This does pre-suppose that new classes await discovery. From an ecological perspective this may not be the case. Given the common evolutionary pathways of microorganisms, likely with most critical targets conserved, the number of targets for possible new drug development is probably strictly limited. On the other hand, rapid whole genome sequence-based target screening has given some leads, but not the expected drugs to combat these targets as yet. So we will need to be patient and remain hopeful. Critically though, we must not base our immediate future practice on the assumption that new classes of antibiotics will emerge. At best, at least for the foreseeable future, we will just have minor improvements on existing agents, still susceptible to the same resistance mechanisms.

New agents and new classes. *The new generation aminoglycosides: Neoglycosides.* Aminoglycoside antibiotics have been used for well over 60 years. These agents are broad-spectrum and are useful both as agents of choice for certain conditions

and also when used synergistically with other antibiotics such as β-lactams. However, they are associated with significant toxicity. Plazomicin (formerly called ACHN 490) is a new compound within this class that is resistant to enzymatic inhibition. It is the first of the new generation aminoglycoside, known as neoglycoside.[22] Thus, bacterial enzymes that inactivate gentamicin do not act on plazomicin although the latter remains susceptible to ribosomal methytransferase.[23] Plazomicin inhibits bacterial protein synthesis and exhibits dose-dependent bactericidal activity. It retains the broad spectrum activity of aminoglycosides including activity against Gram-negative and Gram-positive bacteria. It exhibits synergy with daptomycin and ceftobiprole against MRSA and also against Pseudomonas when combined with cefepime, doripenem, and piperacillin-tazobactam.[24] Plazomicin was also found to have lower minimum inhibitory concentration (MIC) for Acinetobacter when compared with the licensed aminoglycosides.[25] Trials on healthy volunteers have shown no evidence of ototoxicity or nephrotoxicity.[26] It is expected that data from a phase II randomized trial would become available later this year.

Quinolones. Broad spectrum quinolones that retain activity against strains resistant to the current quinolone compounds are under development. One such compound, NXL 101, is primarily an inhibitor of topoisomerase IV. Its spectrum includes Gram-negative bacteria and MRSA. NXL 101 retains activity against strains with mutation in the gyrase enzyme (which is the main target for the fluoroquinolones). Unfortunately, use of NXL 101 is associated with significant QT prolongation but development of safer related molecules remains a possibility.[19,23] Two more compounds, delafloxacin and nemonoxacin, are in phase II studies. Delafloxacin is active against *S. aureus* including MRSA. In contrast to many other fluoroquinolones, delafloxacin retains activity in acidic conditions making it suitable for infections in low pH environment such as the skin, vaginal tract, urinary tract and intracellularly within the phagosomes.[27] A recently published investigation has highlighted the low probability of selection of resistant mutants in MRSA strains exposed to delafloxacin.[28] Nemonoxacin is a non-fluorinated quinolone active against pathogens that cause community acquired pneumonia. It has been found to be comparable to levofloxacin in terms of safety and efficacy.[29]

Another related compound, ACH 702, which belongs to a related class called isothiazoloquinolone, is highly active against MRSA including biofilms but it is being pursued only as a topical agent because of extensive metabolism when given systemically. At concentrations reaching 16 times the MIC, this compound was able to reduce the activity of stationary phase biofilm associated cells of *S. aureus* by a factor of 3 log units.[30] ACH 702 is also active against a wide range of Gram-negative bacilli as well as *Mycobacterium tuberculosis*, which is particularly relevant in the era of drug resistant tuberculosis.[31,32]

Quinazolinediones are active against GyrB and ParE enzymes. These compounds are more active against Gram-positive organisms and less so against Gram-negative organisms because the latter appear to have an efficient drug efflux mechanism that efficiently transports these molecules back to the exterior.[33]

Oxazolidinone. Tedizolid and radezolid are two new oxazolidinone that offer an improvement over linezolid. Tedizolid MICs are lower compared with linezolid for staphylococci, streptococci and enterococci. Both compounds may retain activity against linezolid resistant strains purely on the basis of MIC. Close to 80% of linezolid resistant strains were inhibited by tedizolid at a concentration of ≤ 4 μg/ml.[34] In a recent outbreak of linezolid resistance involving 12 patients, strains of *S. aureus* carrying the plasmid-mediated *cfr* (chloramphenicol florfenicol resistance) gene (rather than the previously described G2675T ribosomal mutation) were isolated. The *cfr* gene, which codes for a methytransferase, catalyzes the methylation of A2503 in the 23s rRNA gene of the large ribosomal subunit thereby conferring resistance to linezolid and several other antibiotics (e.g., chloramphenicol, florfenicol and clindamycin).[35] Tedizolid is active against MRSA that possess the *cfr* gene.[36]

In a double-blind phase 2 investigation, patients with suspected or confirmed Gram-positive infection (a vast majority had *S. aureus* and more than 80% had MRSA infection) were given tedizolid once a day oral doses of 200, 300 or 400 mg (randomized as 1:1:1) for 5–7 d for complicated skin and skin structure infections. Clinical cure rates in excess of 95% were achieved for MRSA as well as methicillin-sensitive *S. aureus* infections in all three dosage groups.[37] Radezolid also shares some of the properties of tedizolid such as activity against linezolid-resistant strains. It has been shown to achieve 11 times higher levels inside macrophages and neutrophils, a property that might be useful when applied to persistent infections with intracellular organisms.[38,39]

In addition to the above compounds, a few antibiotics within this class are being developed as antimycobacterial agents. Sutezolid was shown to be superior to linezolid in terms of antimycobacterial activity.[40] This is probably a much needed breakthrough given that the recent report of total drug resistant tuberculosis from India.[41,42] AZD5847 also possesses activity against mycobacteria[43] and is currently in phase I trial.[44]

New β lactams and monobactams. Ceftaroline is a fifth generation cephalosporin that has activity against MRSA (and also vancomycin resistant *S. aureus*), a property that is obviously unique. It has recently been approved for clinical use by the US Food and Drug Administration. Phase III clinical trials have found that ceftaroline is non-inferior to comparator therapy for the treatment of community acquired pneumonia (FOCUS 1 and 2 trials; comparator: ceftriaxone) and complicated skin and skin structure infections (CANVAS 1 and 2 trials; comparator: vancomycin + aztreonam). Ceftaroline is well tolerated.[45] Ceftobiprole shares this attribute[46] and although it entered phase III trials the antibiotic failed to gain FDA approval.[47]

Aztreonam is the only monobactam licensed for clinical use. However, its use is generally very limited given its spectrum of activity, which includes Gram-negative bacteria only. On the other hand, aztreonam is resistant to the action of metalloenzymes and this has led to a renewed interest in pursuing congeners with broader activity as well as metalloenzyme stability. Such compounds that withstand the action of aztreonam degrading enzymes (e.g., AmpC enzyme and extended spectrum β-lactamase) but retain all the advantages of aztreonam by suitably combining it with traditional inhibitors (e.g., clavulanic acid) have shown limited success so far. However, they offer interesting

ideas for the future. One such compound, BAL 30072 uses an iron uptake system to enter bacterial cells and once inside the cell, it appears to be highly active by inhibiting cell wall synthesis.[23]

New compounds that inhibit β lactamases are also being developed. Avibactam (NXL 104) has a broad spectrum of activity including the KPC enzyme family. Combination therapy with ceftazidime and ceftaroline has been investigated in vitro and the spectrum of the combinations depends upon the spectrum of the β lactam compound. Thus, ceftazidime-avibactam is active against Pseudomonas but not ceftaroline-avibactam combination. The latter combination on the other hand has a very broad spectrum because ceftaroline is active against MRSA (see above).[48,49] Another novel cephalosporin CXA 101 is active against multidrug-resistant strains is undergoing phase 2 trials. Details of this and several other compounds in early stages of development has been discussed by Kanj and Kanafani.[50] While these compounds would certainly increase the choices compared with what we currently have, a "cure-all" remedy e.g., in terms of activity against class A, B and C β-lactamase is still awaited.

Ketolides. Cethromycin and solithromycin are two new ketolides in development. Cethromycin has an orphan drug approval by the FDA for the treatment of bioterrorist threats such as anthrax and plague. Both these compounds are highly active against Gram-positive organisms but modestly active against Gram-negative bacteria. Two phase III non-inferiority studies have been performed comparing cethromycin with clarithromycin. Both studies met the non-inferiority endpoint in the treatment of community acquired pneumonia.[51] However, additional clinical trials are necessary before this agent is approved for clinical use.[47] On the basis of in vitro studies that compare the MIC of solithromycin for various pathogens, it is hoped that its main indication would probably be skin and soft tissue infection and community acquired pneumonia.[52]

Tetracyclines. Tigecycline is a broad-spectrum glycylcycline approved for clinical use. Tigecycline is not a substrate for drug efflux or the ribosomal protection proteins, mechanisms that lead to resistance to tetracyclines. Tigecycline is useful in the treatment of mixed infections if Pseudomonas infection is excluded as it has no activity against this pathogen. However, resistant mutants can be selected during therapy with tigecycline. Omadacycline is similar to tigecycline in its spectrum but unlike the latter, it is absorbed orally. Another new compound is TP-434 which shares several properties with omadacycline.[47]

Newer glycopeptides. Telavancin is a newly licensed lipoglycopeptide. Combined data from the Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia (ATTAIN) trials showed that the cure rates with telavancin was 58.9% compared with 59.5% with vancomycin (95% confidence interval for the difference, -5.6% to 4.3%). In the subset analysis, cure rates were higher with telavancin in patients with monomicrobial *S. aureus* infection although patients with MRSA infection had similar cure rates.[53] Oritavancin is a synthetic derivative of chloroeremomycin. Oritavancin inhibits transglycosylation by binding to the terminal D-alanyl-D-alanine and also binds to the pentaglycyl bridge in the peptidoglycan moiety. Thus it is active against vancomycin-resistant enterococci and VRSA. Oritavancin has long half-life and hence can be administered once daily. Phase 2 trials have been conducted but more trials on oritavancin are expected to be performed in the near future.[54]

Efflux pump inhibitors. These are novel compounds that target the efflux pump in bacterial cell that drive out the intracellular antibiotics back to the exterior. The most promising targets include the resistance-nodulation-division family of efflux pumps. As many as 14 such efflux pumps in this family have been identified in *Burkholderia cenocepacia* and further characterization would be necessary before the target could be exploited in clinical therapeutics.[55,56] Phase I clinical trials were conducted in patients with cystic fibrosis with one such compound designated MP 601,205. However, no further development took place because of toxicity related issues.[57]

Summary

Bacterial evolution is ancient, active and continuous. Indeed, a recent study found that many of the resistance mechanisms have been selected from millions of years. Microbes obtained from samples of Lechuguilla cave in New Mexico, an isolated cave for the past 4 million years, were found to be resistant to 14 different antibiotics.[58] While this is worrying, it also offers hope because promotion of resistance in nature implies existence of mechanisms that inhibit bacterial growth thereby promoting resistance (indeed, thus far unknown mechanisms of resistance such as daptomycin hydrolysis were found in the microbial flora of the cave). On the other hand, uncontrollable use of antibiotics speeds up this process and leads to harm. We have not found an antibiotic to which resistance does not develop. Indeed, it has been possible to generate stable mutants in the laboratory even to the latest compounds such as ceftaroline-avibactam combination.[59] Moreover, resistance is also emerging in fungi and viruses. Echinocandin resistance in *Candida albicans*[60] and oseltamivir resistance in H1N1 influenza virus[61] are well documented. Against this background, the resurrection of older compounds such as the pleuromutilins, which inhibit protein synthesis, is a welcome step.[62] Discovered in 1951,[63] the first pleuromutilin for systemic use, BC 3781, was tested in a phase II trial in 2011.[64] A strategy that promotes research into new as well as known but unutilized compounds, allows efficient development, reduces unnecessary overuse, and limits the spread of bacteria that are already resistant requires partnership, vision and leadership and may significantly counter antibiotic resistance.[65]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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