Anti-infective research and development—problems, challenges, and solutions

In communities and hospitals around the world, the number of patients with antibiotic-resistant infections continues to climb. Our current armamentarium of drugs is gradually becoming ineffective and a new pipeline of robust compounds is needed urgently. In this Forum, we present several perspectives on the problems and pitfalls of drug discovery and development, the challenges faced by the practising physician, and potential solutions to protecting and safeguarding the public health of future generations.

Infectious Diseases Society of America
The Infectious Diseases Society of America (IDSA) noted the lack of new anti-infective agents in late-stage development several years ago, finding that of 506 molecules under development in 2002 at 22 major pharmaceutical and biotech companies, only six were antibiotics. A task force was created to investigate these concerning statistics.

We identified several obstacles to antibiotic development. Anti-infective drug products are less profitable than other types of medicines, particularly those for chronic conditions. Furthermore, once a new antibiotic is finally approved, infectious disease physicians add an additional financial disincentive and urge our general practice colleagues to refrain from using it to help reduce the development of resistance. As a result, many major pharmaceutical companies have decided to focus their research and development efforts elsewhere, leaving the pipeline in this essential field dangerously dry.

In 2004, we offered potential solutions to the US National Institutes of Health (NIH), Congress, the US Food and Drug Administration (FDA), the US Centers for Disease Control and Prevention (CDC), and the pharmaceutical industry to create a financial, research, and regulatory milieu for anti-infective drug discovery and development similar to those for other drug products.

2 years later, however, very little has changed. Our recently updated study identifies six resistant pathogens posing serious threats to patients for which there are few or no drugs in late-stage development. As physicians who treat growing numbers of patients with these infections, we consider this a crisis.

Although the NIH has a role in discovery of new anti-infective targets, mechanisms of resistance, and animal model investigations, it has neither the resources nor experience in the clinical development of antimicrobial agents in the context of multinational, multicentre clinical trials. Furthermore, complex legal issues regarding intellectual property rights, marketing, and ownership of profits in public–private ventures require further resolution before partnerships can flourish in the anti-infective field. We believe the US Congress must act to convince large pharmaceutical companies to return to the anti-infectives market. These companies have the research and development infrastructure required, and a proven record of bringing new anti-infective agents through clinical trials and past government regulatory requirements—experiences and resources that are essential in this time of great need.

US lawmakers have responded to some extent by proposing a federal authority, the Biomedical Advanced Research and Development Authority (BARDA), to be situated within the US Department of Health and Human Services, which would provide a US$1 billion-per-year shot in the arm to infectious disease product development. The US House of Representatives passed the legislation in October, 2006. Senate action is pending. The intent is to help smaller companies shepherd promising countermeasures (vaccines, drugs, diagnostics) intended to protect against “public-health emergencies affecting national security” through the complex, expensive, and often difficult period between laboratory success, clinical trials, and manufacturing development. In its current state, the bill would cover biodefence and pandemic influenza countermeasures. IDSA has endorsed this concept, but has urged that the “countermeasures” definition be broadened to address infections that threaten the lives of a significant number of people annually (eg, meticillin-resistant *Staphylococcus aureus* [MRSA]), not just those affecting national security. Thus far, our request has been rebuffed. Should the definition remain unchanged upon the bill’s passage, IDSA will advocate that BARDA funding be targeted toward broad generic approaches and technologies that will be immediately applicable to many different diseases and agents. We will also continue to caution that BARDA funding should not come at the expense of other infectious diseases research and public-health projects.

The IDSA task force has worked closely with members of Congress to draft other supportive legislation that some financial analysts believe will provide the appropriate incentives, representing a reasonable return on the substantial investment necessary to bring novel anti-infective agents to the patient. This legislation includes, among others, tax credits for research, development, and manufacturing expenses, expanded intellectual property rights, and the creation of a commission to set antimicrobial discovery priorities. There has been intense political debate between those who believe these incentives to be fair and necessary to spur research and development, and those who oppose them as gifts to industry.

IDSA has also promoted the designation of novel anti-infective agents as “orphan drugs”. Congress and the
FDA have long accepted the concept that drugs for a relatively small portion of the population should enjoy certain financial incentives, since the market and the profits for these agents will never be great. Although patients infected by certain multidrug-resistant pathogens clearly meet the regulatory definition proposed for orphan drug development, industry has not pursued this approach. It is not clear whether this is because of specific legal or economic considerations.

We have found the FDA willing and interested in moving new anti-infective development forward as efficiently as possible. In 2004, the agency published the Critical Path document, designed to smooth the path to new drug development. However, antibiotic development guidelines, promised several years ago by the FDA for bacterial meningitis, acute bacterial sinusitis, acute bacterial otitis media, and acute exacerbation of chronic bronchitis, are long overdue. These guidelines must be standardised and transparent to achieve consistency, and are essential for industry to know the extent of investment, so that it can be compared with anticipated revenue if the agent is approved. Without written guidelines, companies are more inclined to commit investment dollars to areas of drug development where less ambiguity exists. We believe the FDA must act swiftly to end the ambiguity.

The hospital physician

As the problem of antibiotic resistance in the community, nursing homes, chronic care facilities, and particularly acute-care hospitals grows ever more severe, physicians are finding it increasingly difficult to deliver effective treatment. The need to administer the “right” antibiotic as soon as a severe infection is recognised—and before culture results are available—poses additional concerns. Effective treatments for empiric and pathogen-directed therapy are in decline at a time when the need for new “smart” and effective antibiotics has become greatly pronounced.

Currently, nosocomial extended-spectrum beta-lactamase (ESBL)-producing Gram-negative organisms can be found in nearly every institution. Older penicillins, semi-synthetic penicillins, and first and second generation cephalosporins are becoming increasingly ineffective in treating nosocomial infections since they are inactivated by the beta-lactamase producing nosocomial pathogens. Physicians are increasingly forced to use the carbapenems and fluoroquinolones as first-line therapy. The situation with resistant nosocomial Gram-positive pathogens, including *Acinetobacter* spp, *Stenotrophomonas* spp, and *Pseudomonas aeruginosa*, are global pathogens. These strains are frequently multidrug-resistant, necessitating the use of agents such as the polymyxins (eg, colistin) in systemic and topical (intrabronchial, intrapulmonary) administration forms. This therapy is associated with lower rates of successful bacteriological and clinical outcome, together with increased toxicity—the very same reason these agents were previously abandoned.

The situation with resistant nosocomial Gram-positive pathogens is not much better. Their prevalence as pathogens of primary bacteraemia, endocarditis, and hospital-acquired and ventilator-associated pneumonia (HAP and VAP, respectively) has increased exponentially in recent years. The appearance of vancomycin-resistant enterococci and nosocomial multidrug-resistant *S aureus* and *Staphylococcus epidermidis* has also curtailed the available therapeutic arsenal, whereas the newer agents (oxazolidinones, lipopeptides, newer glycopeptides, and newer cephalosporins for MRSA) are either expensive, hampered with adverse effects, or have not yet been introduced into clinical practice.

At the same time, community acquired-MRSA (CA-MRSA), multidrug-resistant *Streptococcus pneumoniae*, macrolide-resistant group A streptococcus, and viridans...
group streptococci have complicated the situation even further, forcing community physicians to abandon the beta-lactams and macrolides as the major therapeutic antibiotic classes and resort to alternative agents such as fluoroquinolones and oxazolidinones.

What is it that the clinician is missing? Certainly, new effective antibiotics against Gram-negative organisms—whether carrying ESBL or multidrug-resistance—are badly needed, and the lack of news on this front is rather depressing. In view of the very slow development of new anti-Gram-negative agents interacting with new targets, could older, existing agents be modified to allow creation of more potent agents; agents with easy applicability or lower toxicity, or both? Development of newer aminoglycosides or detoxifying available aminoglycosides (perhaps using liposome technology) seems to be an achievable aim. Agents that block Gram-negative toxins, as well as other virulence factors including quorum-sensing molecules, might also be an attainable target. Development of newer versions of existing agents with greater affinity for known targets (eg, penicillin binding proteins, DNA/DNA gyrase, 30S and 50S ribosomes) could allow the creation of more pharmacodynamically potent agents that slow the rate of resistance increase. Antibiotic agents with pharmacological characteristics that allow penetration and efficacy in sanctuaries such as the bronchial mucosa and epithelial lining fluid, and are active against organisms complicating chronic bronchitis and cystic fibrosis, would be of tremendous advantage. Studies of newer agents active against Gram-positive pathogens, including those resistant to vancomycin (eg, vancomycin-resistant enterococci and vancomycin-resistant S aureus) are progressing adequately, and hopefully will lead to the introduction of several new effective agents against these organisms.

Lack of new antibiotics requires re-evaluating and re-investing in monoclonal antibodies, bacteriophages, probiotics, and ways to augment innate immunity. With few new antibiotics in the pipeline, perhaps we need to go back and re-evaluate our dosing schedules, durations of treatment, and how and when to use combination therapy to achieve clinical success and prevent resistance from occurring. Should the pharmacodynamic targets for the management of critically ill patients in the hospital setting (eg, HAP and VAP) be aggressively increased to attain free drug time above minimum inhibitory concentration (MIC) of 100%, and not around 50% for beta-lactams, and 24-hour area under the curve/MIC of 250 or more for fluoroquinolones and aminoglycosides? These greatly increased doses of antibiotics will increase adverse effects, but might offset the development of resistance and might increase bacteriological and clinical success. New knowledge on appropriate durations of antibiotic therapy for particular infections is urgently needed. Although large steps have been taken in shortening the treatment durations of VAP, intestinal infections, right-sided endocarditis, and urinary tract infections in women, the majority of recommended treatment durations are based on expert opinion only. We also need to acknowledge that our understanding of when and how to best use combination antibiotic therapy is lacking. Additionally, it is crucial to continue to reduce the inappropriate use of antibiotics for viral respiratory tract infections in community practice, reduce the near 40% inappropriate use of antibiotics in hospital settings, and reduce inappropriate antibiotic use for non-humans. Reduced exposure of the host and the environment to unnecessary antibiotics may induce and select for less resistance.

Will it be possible to have antibiotics solely restricted for hospital settings and others restricted for community settings? With the current frame of acceptable toxicities the answer is probably no. With the lack of new antibiotic development and the rising need for effective agents, we might have to decrease the acceptable safety bar for antibacterials that are strictly hospital drugs—eg, polymyxins, certain fluoroquinolones (clinafl oxacin hydrochloride), and abandoned aminoglycosides—while keeping the safety bar high for community-used agents. Evidently, the lack of effective antimicrobials in hospitalised patients with nosocomial infections is rapidly nearing a crucial point that needs to be addressed with both short and long-term solutions.

**Conflicts of interest**

ER serves on the advisories of Bayer, Theravance, Pfizer, Replydine, Wyeth-Canada, King Pharmaceuticals, InterMune, Rosetta, and BiondVax. Has received research grants from Daiichi, Bayer, Theravance, Sanofi-Aventis, and Cubist. GGZ has received research grants from Abbott, Affiniaum, Ortho McNeil, Pfizer, Sanofi-Aventis, and Wyeth.

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**A primary care physician**

In primary care settings, respiratory infections including sinusitis, bronchitis, common cold, influenza, and pharyngitis could account for as many as 75% of daily and return visits to the clinic. Much of the problem of resistance is probably associated with combined inappropriate prescribing and increased patient demand for a course of antibiotics from their health-care providers. The CDC report that as many as 10 million courses of antibiotics might be prescribed annually for viral conditions that will, of course, not respond to antibiotics.

Piney Flats, Tennessee, USA, is a rural community within the “Tri-Cities” Tennessee area equidistant between...
Johnson City, Kingsport, and Bristol. Interestingly, although patients in this community live only 8 miles (13 km) from any of the three larger city areas they prefer to stay within the Piney Flats community for their health care. This consists of a population of about 4000 people with another 35000 living in any of the three larger city areas for an overall catchment of about 100000. The practice has three physicians and two health-care providers, a nurse practitioner, and a physician assistant serving about 5000 patients from the surrounding towns. The group sees roughly 20–30 patients per day per provider, mainly in the 20–30 and 55–70-year-old age groups. The region is heavily agricultural but has a growing high-tech and chemical industry. As a result, tobacco-smoking is very common with a high proportion of patients in the practice consuming three to five packets per day. Indeed, tobacco smoking is occurring earlier than ever before and more commonly among young females, thus shifting the patient types we often see with respiratory problems. Perhaps it is this risk factor and the repeated antibiotic exposures that have contributed to the local antibiotic resistance rates, which according to the CDC are among the highest in the USA. Recent data suggest high level penicillin resistance to be over 10%, with even higher rates of resistance to macrolides and other commonly used drugs. It is against this background that I run my daily primary care practice.

A classic and frequent case in point seen in this setting is a patient presenting with cough, sore throat, rhinorrhoea, and malaise. Rapid assays for influenza A and B and group A beta-streptococcus return as negative, and patients are prescribed supportive therapy for diagnosed viral syndrome or a common cold. Patients frequently return within 2–3 days with little improvement in symptoms and request antibiotics. This is the point at which patient education is paramount, otherwise as providers we give in to patient demand and worsen the problem of antibiotic resistance in our communities. Unfortunately, despite our best efforts, many patients might at this point present to local emergency departments with a second request for antibiotics, which they receive and thus go home satisfied, thereby ultimately perpetuating the problem for primary care providers.

There is also the frequent issue of patient “allergies” to certain antibiotics such as nausea, listed indiscriminately both in patient charts and pharmacy records. This event is frequently seen with aminopenicillins and macrolides, and although not a true allergic response, it might force the prescriber to give broad-spectrum, high-potency drugs for simple or narrow-spectrum conditions.

In relation to respiratory-tract infections, the most frequent resistance noted at this rural practice is in the form of treatment failures in sinusitis and acute exacerbations of chronic bronchitis. At this rural care clinic, we often see hastened follow-up visits because of either no improvement or worsening of symptoms after courses of amoxicillin, macrolides, or doxycycline given as first-line courses of therapy (the standard first-line recommendations of the Sanford Guide To Antimicrobial Therapy). Unfortunately the issue with most of these first-line empirical therapies is the length of therapy being two to three times a day for 10–14 days allied with growing resistance. The more clinically effective subsequent second-line courses of therapy observed with fluoroquinolones are causing a definite shift to using newer agents such as gemifloxacin mesilate or even levofloxacin more often as a first-line choice. This is particularly true for our large population of heavy tobacco smokers in the region who have frequent episodes of acute bacterial exacerbations of chronic bronchitis. The shorter treatment courses—once-daily dosing of fluoroquinolones—also enhances patient compliance and provides better clinical outcomes. For this patient population, gemifloxacin mesilate is probably the more efficacious antibiotic and might avoid resistance emergence and unnecessary follow-up visits.

Although we in primary care are unable to monitor antibiotic resistance, we are aware of the trends among respiratory and urinary pathogens, and are concerned that our therapeutic options could become limited since research and development in this field appears to be decreasing in favour of more chronic medications. Education of patients, physicians, and health-care providers about the paucity of new antibacterials and how better to use those we presently have is urgently needed along with renewed encouragement to those companies committed to bringing new antibiotics to the clinic.

Conflicts of interest
I declare that I have no conflicts of interest.

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GSK—a major pharmaceutical company
Neither AIDS, malaria, nor even pandemic influenza heads the list of “pharmaceutical gaps” compiled by WHO. That top position goes to infections caused by drug-resistant bacteria, which raises the question about the commitment that industry has to take to combat bacterial resistance.

Why isn’t antibiotic discovery very fashionable these days? Clearly there are financial considerations for publicly traded companies who must deliver for their shareholders. Some aspects of the antibiotics market detract from commercial returns: the short-term use of nearly all antibiotics and—perhaps increasingly—a tendency by physicians to refrain from prescribing new antibiotics so as to keep them in reserve until older drugs fail. At the same time, companies must consider other medical needs—various scourges put competing claims on research and development budgets. Recently,
systemic drugs for infection accounted for about 8% of all drugs brought to initial clinical studies. By contrast the figure for drugs for cancer and immunological disorders is just over 20%.\(^a\)

The specific scientific challenges related to antibacterial research are less widely recognised. To be potentially a broad-spectrum antibiotic, a single compound must inhibit the growth of several bacterial species, all of which have different molecular targets, different membrane permeabilities, and different metabolic pathways. Making such a compound is a profound chemical challenge: consider that the phylogenetic divide between Gram-negative and Gram-positive bacteria exceeds that between human beings and paramecia. Any antibiotic must also show an acceptable side-effect profile at the high blood levels typically required to ensure effectiveness against the least susceptible organisms. Fortunately, the generally acute course of bacterial infection in individual patients allows for a rapid assessment of antibiotic efficacy. Even so, enrolling enough patients into clinical studies directed at resistant bacterial strains is still another challenge, since outbreaks of the infections cannot be anticipated.

There is already an urgent need for new antibiotics, in view of the accelerating spread of resistance, newly emerging infectious agents, and the menace of bioterrorism. GlaxoSmithKline (GSK), for its part, has had an active programme of drug discovery for infectious diseases and has recently announced the creation of a dedicated Centre of Excellence for Drug Discovery in this area. Research into bacterial infections figures importantly in the scope of this centre, as does research on diseases endemic in poor countries. We believe several markets will continue to reward innovation in discovering and developing antibiotics. Where market incentives are lacking, we engage with academia, government, and philanthropies to meet our common responsibilities. We have formed partnerships with both the Global Alliance for TB Drug Development and the Medicines for Malaria Venture. Our partners help to support 55 scientists working exclusively on tuberculosis and malaria drugs. GlaxoSmithKline contributes a similar number of scientists, laboratories, and our discovery and development experience. We will make resulting medicines affordable to those most in need.

As for the science, we are progressing in what might be considered the old-fashioned way, with strong medicinal chemistry and the other disciplines focused on development potential. The role of chemists—I say this as a biologist—can hardly be overstated. Even once a lead chemical series is identified, another 3 years or more could be required to synthesise a derivative with the requisite properties for development. One example is the class of pleuromutins, isolated from the fungus Pleurotus muticus in the 1950s and studied in their semi-synthetic forms into the 1980s. Notwithstanding that long history, the class never came into human use, owing to its poor oral bioavailability. During the past 5 years, however, we have overcome this and other obstacles by committing a large team of chemists to the task. The results are three pleuromutins now in clinical studies, all of them oral, broad-spectrum agents for diseases such as respiratory tract infections. They inhibit protein synthesis by binding to a novel site on the bacterial ribosome. We have another pleuromutin for topical use, retapamulin, which is under regulatory review as a treatment for skin infections caused by \(S\) aureus or \(S\) pyogenes. What is more, we have advanced three other orally available, novel antibiotic classes into various stages of preclinical discovery or development.

A decade ago, the hope was that genomics would provide for drug discovery a trove of broadly useful bacterial targets. Although genomics has greatly informed bacterial phylogeny and physiology, it has not yet led to a marketed antibiotic. Nor has automated screening of bacterial targets against vast chemical libraries met early expectations: the “hit” rate in these screens has been lower than in other therapeutic classes, arguably because these libraries are historically skewed toward mammalian targets. The way towards a new medicine will always entail learning from previous mistakes and will demand sustained commitment. Our heritage in antibacterial research dates from the early penicillins. We intend to do our part in the future too.

**Conflicts of interest**

I am an employee of GlaxoSmithKline.

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**Cubist—a small pharmaceutical company focusing on hospital infections**

While some large pharmaceutical companies are leaving research and development of anti-infectives for seemingly greener pastures in chronic medications—surely a worrying trend—small pharmaceutical companies are stepping into the breach and providing novel, efficacious products for the treatment of patients infected with resistant organisms.

Cubist Pharmaceuticals, Inc, provides one such example. Cubist’s drug daptomycin, the first antibiotic from a class of anti-infectives called lipopeptides, was approved in November, 2003. Daptomycin is an intravenous antibiotic targeted at treating \(S\) aureus, including MRSA, and other Gram-positive infections. The antibiotic was originally discovered by Eli Lilly, but the company discontinued work on the drug in 1991 because of toxicity problems. Seeing an opportunity in the increasing incidence of MRSA and
increasing resistance to the last-resort antibiotic vancomycin, Cubist in-licensed the compound in 1997. Because Eli Lilly provided no drug substance suitable for clinical trials and there needed to be a change in dosing, the drug had to be made again and the toxicokinetics and clinical trials repeated and improved—essentially a development restart. Cubist has therefore shown that small pharmaceutical companies can take a nascent product from early development through to commercialisation.

For small companies to succeed both in development and commercialisation, it is important to choose areas of unmet need. Acute and serious infections without adequate available treatment, combined with the hospital treatment setting, provide a particularly favourable risk-to-reward balance.

In terms of risk, the development path for an acute indication in a hospital setting provides a number of benefits. Typically, trial sizes are smaller than those in an outpatient setting, in the range of several thousand patients. For non-serious outpatient indications, much larger trials and safety databases are necessary; it is much more difficult for small companies to afford and to implement such operations. Because of the high unmet need and the seriousness of the condition, regulatory bodies are willing to work carefully with sponsors. This cooperation ensures that endpoints will be agreed and avoids regulatory problems, and as a result avoids the delays and uncertainty that are typical in many drug development programmes. Recently the FDA, the IDSA, and small pharmaceutical companies worked together to successfully streamline the regulatory process. The FDA was cooperative in working with Cubist to develop daptomycin. This relationship not only enabled Cubist to develop daptomycin expeditiously but also allowed the company to study daptomycin in high risk indications that others—even big pharma—were not willing to undertake.

In terms of reward, the hospital-based acute infection also provides important advantages in commercialisation. The prescribing bodies in hospitals can be targeted in a much more specific way than practitioners in the community, meaning that a large and expensive marketing team is not necessary. Close liaison with practitioners leads to a specific knowledge—enabling targeted education of appropriate uses of the drug. The small base of targeted prescribers also means the drug’s benefits can be communicated more effectively.

Beyond the reasons given above, the key ingredient of all successful biotechs is an experienced group of drug developers. Typically, these are people that have taken a product all the way from discovery to the market, and are aware of the potential challenges and pitfalls. Ironically, this experience is normally gained at big pharma and then applied again at small biotechs.

The first product cycle of successful biotechs in infectious disease has largely come from compounds initially discovered in big pharma. However, as big pharma exits antibiotic discovery, the next cycle could include products discovered in biotechs. These will consist of both entirely novel classes of antibiotics and analogues of existing antibiotics. New chemistry and molecular biology mean that existing antibiotics can be developed in new ways, potentially creating drugs that microbes are not yet resistant to, or drugs with better pharmacokinetics and safety levels. To combat the problem of resistance, novel classes of antibiotics that microbes have not yet encountered are required.

Powerful new screening techniques can be used to find such agents, which will not have the problems of cross-resistance that older, recycled agents have. As the screening approach gets more widely adopted, because of the sheer number of molecules screened, finding “novelty” is becoming harder. Yet a combination of good screening techniques and looking in the right places, such as natural product banks, should yield new classes of antibiotics. Pfizer managed it in the 1980s with the oxazolidinones (linezolid) and Lilly/Cubist with lipopeptides (daptomycin). Biotechs are well positioned to perform discovery in these areas. Cubist is continuing to explore both the lipopeptides and other new potential classes to provide treatment for clinical needs. This will not happen overnight, of course. Patience is still a virtue in antibiotic research. The process is still going to take 5–8 years and cost US$500–700 million, regardless of whether it is a small or big pharmaceutical company doing the work.

**Conflicts of interest**
We are employees of Cubist Pharmaceuticals, Inc.

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**Small pharmaceutical company approaches to community infections**

There is a paradox when considering the needs and outcomes for developing antibiotics for community-acquired bacterial infections. From a public health perspective it would seem logical to assume that the escalating incidence of resistance is an issue that needs to be addressed. Yet clinical practitioners do not seem to regard the effects of resistance as a major problem. Beyond the reasons given above, the key ingredient of all successful biotechs is an experienced group of drug developers. Typically, these are people that have taken a product all the way from discovery to the market, and are aware of the potential challenges and pitfalls. Ironically, this experience is normally gained at big pharma and then applied again at small biotechs.

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entities, but are also committed to sizeable clinical trial programmes that will enable the submission of new antibiotics to the regulatory agencies.

To be defined as small, a company has to be either commercially based or research-based, with less than 300 staff. Small companies usually have financial resources or a cost enterprise value of less than $500 million (often associated with a revenue flow of $100–200 million/year), and less than three compounds in phases II or III of clinical development. Clearly the focus of staff will depend on whether the organisation is purely research oriented or sales driven.

It is essential to consider that a potentially large opportunity for a resistant infection exists in the community setting. However, the clinical consequences in this setting are less clear and less dramatic than a failure in a hospitalised patient. In the community, resistance could cause a simple failure to respond to the drug in the usual period, because the host defences might be adequate to enable clinical cure, or the delay could mean the patient calls the practitioner requesting or demanding another course of antibiotics. However, it is very difficult to quantify the consequences of transmission of the resistant bacteria, such as multidrug-resistant pneumococci, especially in the at-risk populations in nursing homes or day-care centres. In the face of such ill-defined consequences, few practitioners are confident in using the newer agents—which are perceived to be more expensive—especially if the managed care organisations are unconvinced of the cost–benefit of such an approach.

Moreover, in the current primary care setting, where more than 230 million antibiotic prescriptions are written annually in the USA, the ability to influence the prescriber is driven by the number of representatives who see the physician each day. It is in this busy setting that the practitioner has the proverbial 3 min to diagnose, manage, and treat the patient. The more regular the message from the large pharmaceutical company, the higher the likelihood of their agent being prescribed. Thus small pharma has to focus on very specific infections or indications that are more likely to lead to prescriptions, which in turn will provide revenue to support both future research and sales force expansion.

In the USA, community-acquired infections are mainly respiratory in nature such as bronchitis, sinusitis, pneumonia, and tonsillo-pharyngitis. Antibiotic resistance is increasing among the more common aetiological agents in these illnesses, but until increased hospitalisations, lost productivity, or even mortality are documented, we will have to wait and see if the recent efforts by two small pharmaceutical companies—namely Oscent (Waltham, MA, USA) and Replidyne (Louisville, CO, USA)—are successful.

Oscent and Replidyne have taken different approaches to tackle the problem of educating prescribers about the consequences of antibiotic resistance. Oscent, which manufactures gemifloxacin mesilate, has created a small, highly targeted primary care-based sales team of 250 representatives. This team has been concentrated in the major metropolitan areas and focuses on visiting the busier doctors. Replidyne, which manufactures faropenem medoxomil, is to form a marketing partnership with a fairly large pharmaceutical company with around 1000 sales field personnel. Both Oscent and Replidyne continue to extend the range of indications of the two drugs developed to combat resistant pathogens. They both have clinical development programmes in place for other “resistance-buster” drugs, but their focus is on specific hospital pathogens—namely ramoplanin for C difficile and REP 8839 for MRSA control, respectively.

Can small pharma be successful in developing antibiotics for community-acquired resistant infections? They can. By identifying possible candidates either in early post phase I or in the much later “virtual new drug application” stage, which for whatever reasons are no longer of interest to big pharma (certainly this is applicable to both gemifloxacin mesilate and faropenem medoxomil). As a result, a narrow product approval can be obtained in a rapid and focused manner. Once the drug has been shown to be efficacious and safe, small pharma can either carefully target the busiest prescribers, or align with a larger partner who will promote the new antibiotic among the usual three or four primary care pharmaceutical portfolios in a more conventional approach.

Clearly, some good fortune, good science, and astute business sense are needed for success as a small, tightly resourced company. Whether these are the ingredients needed to base a continuous development pipeline for the treatment of resistant community-acquired bacterial infections remains to be seen. For now two small entities have dared to go where the larger ones feared to tread.

**Conflicts of interest**

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Einstein said that in the middle of every difficulty lies opportunity.” The difficulty we face is the inevitable emergence of diseases caused by pathogens to which currently available therapies may be less effective. However, in the midst of this difficulty is the opportunity to re-examine our approaches to infectious disease therapeutics and antimicrobial drug development.

The first issue to consider is a re-evaluation of the definition and reporting of “resistance”. The public-health concern is that resistance in vitro may reflect
increased mortality and/or morbidity in patients. In some cases, there is a lack of evidence that “resistance” affects clinical outcomes—eg, in vitro macrolide “resistance” in *S pneumoniae* has had little proven impact on clinical outcomes even in serious diseases such as pneumonia. In other diseases, such as otitis, sinusitis, and acute exacerbations of chronic bronchitis, there is a high rate of spontaneous resolution without antimicrobial therapy. In these diseases where the benefit of antimicrobials compared with placebo appears small in disease caused by susceptible pathogens, the effect of resistance appears commensurately small as well. Therefore, the use of a single set of MICs to categorise interpretive criteria as “susceptible”, “intermediate”, and “resistant” for an organism/drug combination, regardless of the disease, may not accurately reflect clinical outcomes for patients.

It is imperative to define resistance based on data from studies that measure clinical outcomes in patients in the disease setting where clinicians use the drug. Although in-vitro data and pharmacodynamic modelling can help frame the discussion, these methods do not take into account the effect of the immune system and other variables at the site of infection. Moreover, even patients with disease caused by susceptible organisms fail therapy, especially in serious diseases in patients with multiple comorbidities, making the interpretation of “case reports of failures” challenging. Inaccurate definitions of resistance, even if considered “conservative”, may lead to over-estimation of resistance prevalence with resulting potential prescribing of drugs with increased toxicity or unproven effectiveness.

As noted by others in this series, there are economic and scientific reasons for the shortfall in antimicrobial development but all agree on the need for new therapies. However, fewer drugs with superior efficacy in the treatment of serious diseases caused by resistant pathogens would be preferable to more drugs without proven superiority or proven effectiveness in serious diseases. An evaluation of past approvals shows 24 of 29 FDA-approved antimicrobials in the 1980s were beta-lactams, many without improved efficacy or safety compared with available drugs. All were approved based on non-inferiority trials, the basic design of which attempts to show how inferior a new treatment might be compared with proven effective treatments. In the 1990s, antimicrobial development focused on quinolones. Five of 12 members of this class are no longer available for patients.

Appropriate use to preserve the utility of current drugs is essential. Use of antimicrobials for self-resolving diseases, many of which may not be bacterial in origin, drives the problem of antimicrobial resistance. However, since potential sales for drug sponsors are greater in the outpatient arena, there is a natural tendency to desire to develop drugs for that population. The hypothesis that antimicrobial approvals for self-resolving community-acquired infections will spur the development of drugs for more serious diseases has been tried and failed. In the past 25 years, FDA has approved approximately 70 New Drug Applications for self-resolving diseases, yet this has not resulted in a boom in antimicrobials for serious diseases. The good news is that the two new drug classes introduced in the past 6 years exceeds the number of new classes approved in the past 40 years combined.

The need for better drugs implies measurable superiority of newer therapies compared with older, presumably less effective therapies. In the setting of antimicrobial resistance, non-inferiority trials will not accomplish this goal. When a drug is proven superior in randomised clinical trials, there is little discussion by clinicians of reserving use of the drug. For instance, voriconazole became the drug of choice for invasive aspergillosis when it showed superiority to amphotericin B.

**Panel: Opportunities for advancement in antimicrobial trials to help provide better evidence related to effectiveness and safety**

- Clinical trials should have a clear objective: antimicrobial trials are based on the evaluation of the treatment, prevention, or diagnosis of a disease in patients, not the evaluation of in vitro activity against a specific pathogen.
- Trials should have a quantitative comparison with a control: regulators need to specify clearly when non-inferiority trials are not acceptable, as in the study of sinusitis, bronchitis, and otitis. Regulators should outline clearly the data sponsors should provide to justify the use of non-inferiority trials in diseases where this trial design is acceptable.
- Trials should ensure that patients have the disease under study: ability to diagnose infections at the point of care would streamline enrolment in trials of patients whose disease is caused by resistant pathogens and allow the study of narrow-spectrum drugs.
- Trials should ensure baseline comparability of patients: randomisation is not foolproof and baseline imbalances still can occur. Choosing the appropriate population is a matter of balance between a population that is heterogeneous enough to extrapolate the results of the trial to general practice but homogeneous enough to obtain useful results.
- Trials should attempt to minimise bias: investigators should double blind trials whenever possible. Microbiological testing results should also be blinded (or partly blinded) to obtain the data to define “resistance”.
- Trials should have well defined and reliable endpoints: endpoints should measure outcomes that are clinically relevant to patients and capture the net harms and benefits of a therapy on those outcomes. Patient-reported outcomes can provide a more patient-centred and perhaps more sensitive way of measuring clinical outcomes for patients. Endpoints based on investigator discretion, “cause-specific” outcomes related to infection and measurement of biomarkers instead of clinical outcomes may be misleading.
- Trials should have an appropriate analysis of the data: investigators should evaluate the information obtained from a trial in a way that allows an estimation of the uncertainty regarding the conclusions.
- Trials should provide an adequate evaluation of the safety of a medical intervention: an adequate evaluation of the safety of a medical intervention needs a database of sufficient size. Vigilant post-marketing studies should become standard practice.
been made. However, despite FDA, US government, and industry working together to the importance of various organisations including NIH, broad-based use of these funds. They also acknowledge IDSA recognise this drawback and are advocating a more Ethan Rubinstein and George Zhanel, and Michael Tino. is unlikely to include the types of organisms discussed by IDSA identifi ed six top-priority dangerous pathogens for in the arena of public-health emergencies. However, this which could fund smaller company research initiatives developments include the initial approval of BARDA, some of the commercial problems. Some recent legal which there are few or no drugs in development, further compounding the urgency of the situation. Over the years IDSA have actively offered potential solutions to some of the commercial problems. Some recent legal developments include the initial approval of BARDA, which could fund smaller company research initiatives in the arena of public-health emergencies. However, this is unlikely to include the types of organisms discussed by Ethan Rubinstein and George Zhanel, and Michael Tino. IDSA recognise this drawback and are advocating a more broad-based use of these funds. They also acknowledge the importance of various organisations including NIH, FDA, US government, and industry working together to drive new antibiotic development. However, despite verbal willingness to collaborate very little progress has been made. This kind of uncertainty only increases the nervousness of drug sponsors who are still involved in antimicrobial development or wish to enter this field. Adequate and well-controlled trials for measuring effectiveness are defi ned by seven criteria in US regulations. These same trials provide the evidence for evaluating the preliminary safety of drugs. There are several opportunities for advancement in antimicrobial trials to help provide better evidence related to effectiveness and safety in a more effi cient manner (panel). The issues with antimicrobial resistance are societal issues. It will take a uniﬁ ed approach and strong leadership from all sectors of society to provide solutions. Government agencies should provide adequate resources to the Interagency Task Force on Antimicrobial Resistance to fulﬁ l the Public Health Action Plan to Combat Antimicrobial Resistance, which includes a section on product development. We must use the challenges before us as an opportunity to advocate for patients to both protect and promote public health. Conflicts of interest I declare that I have no confiicts of interest.

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Bad bugs still need drugs
The concern over the future of antibacterials is growing. We see from this collection of viewpoints that efforts are being made to address the problem of antibiotic-resistant infections, but is it too little too late? John Bradley, Robert Guidos, Steve Baragona, and John Bartlett from the IDSA have identifi ed several obstacles hindering drug development. Furthermore, in early 2006 IDSA identifi ed six top-priority dangerous pathogens for which there are few or no drugs in development, further compounding the urgency of the situation. Over the years IDSA have actively offered potential solutions to some of the commercial problems. Some recent legal developments include the initial approval of BARDA, which could fund smaller company research initiatives in the arena of public-health emergencies. However, this is unlikely to include the types of organisms discussed by Ethan Rubinstein and George Zhanel, and Michael Tino. IDSA recognise this drawback and are advocating a more broad-based use of these funds. They also acknowledge the importance of various organisations including NIH, FDA, US government, and industry working together to drive new antibiotic development. However, despite verbal willingness to collaborate very little progress has been made.

Rubinstein and Zhanel describe the problems facing the hospital-based prescriber. Rapidly evolving bacteria in the hospital setting and constantly moving clinical scenarios have presented us with some almost untreated pathogens including P aeruginosa, S aureus, and Acinetobacter spp. The authors suggest it may be time to revisit old drugs either in new formulations or new combinations as these resistant pathogens out-strip our current armamentarium. However, from the pharmaceutical and regulatory perspectives, who will provide the fi nances and other resources to develop old drugs such as colistin to the proposed regulatory standards? One approach to conserve the drugs we do have is to restrict some antibiotics to hospital use alone, thereby decreasing some of the selective pressure exerted by community-based prescribing. This approach is an interesting idea but with broad-based formularies, such restrictions may need to be draconian in their implementation.

Tino, a busy family practitioner, appreciates the issues of emerging resistance but contends that besides new agents being prescribed appropriately it is essential that the public be made more aware and better educated about when antibiotics are needed. Although some countries have embraced these educational initiatives
very aggressively, such as the UK and Belgium, other countries have left these initiatives to inadequately funded government groups or other organisations perceived to have a responsibility in this area, such as health-care insurance companies in the USA. Tino also raises some key issues around poor compliance to drug regimens by patients and the need to get the patient better and back to normal sooner by using newer agents in certain patient groups. He also recognises that in an attempt to eradicate the pathogen more efficiently, it might be beneficial to use more potent antimicrobial agents, a concept yet to be more widely accepted, as noted by John Powers in his piece. However, while we wait for the evidence to be collected to support Tino’s position we may be “throwing the baby out with the bath water” as the threat of resistance overtakes our innovation. From a clinical standpoint resistance does have an impact and requires urgent attention for both community and hospital-acquired infections, but who will take this issue on?

In the past 5–8 years, big pharma has exited the drug development stage at a remarkable rate. The closure of antibacterial research groups, the “spinning off” of small groups or organisations to focus on anti-infectives, and the general reduction or cessation of promotional efforts in antibacterials are all clear indicators of withdrawal from this field. Furthermore, the imminent patent expiry of several blockbusters reduces the allure for big pharma to retain its involvement. Interestingly many of these companies including Lilly, Bayer, Bristol-Myers Squibb, and others, who have publicly admitted to not pursuing antibiotic research, all declined to explain why they took this course of action in this Forum. Several companies have sold off their assets, such as Lilly with their glycopeptide collection, in the hope of recouping some of their initial outlay, while others have terminated many of their own programmes but in-licensed less risky compounds in the hope of remaining viable in this area—for example, Johnson & Johnson with both doripenem and ceftobiprole for hospital-related infections.

The response from industry staying in the field is variable. Clearly some companies are more committed than others. Among big pharma, GSK has a long and successful history of antibacterial research and development and are continuing to bring new drugs to the clinic such as retapumulin (currently in phase III for skin infections). Indeed, GSK has established a Center of Excellence for Drug Discovery with a focus on bacterial infections. This centre is in response to the realisation that efforts in genome research, despite a huge financial investment did not bear the anticipated fruit.

By contrast, small companies such as Cubist, Oscient, and Replidyne have obtained partly developed big pharma compounds and taken them to New Drug Application submission or beyond. Drugs for hospital-acquired pathogens comprise a smaller market opportunity but require a smaller resource to develop and promote the new entity. Alternatively, community focused antibiotics aimed at the much larger, but more difficult to access infections caused for example, by resistant pneumococci, need a much larger and intensive sales and marketing effort to recoup the substantial outlay of research and development. It is ultimately up to the company shareholders to decide if they want to pursue such a drug.

In addition to the efforts by industry, changes in the regulatory environment in terms of the drug approval process need to be taken globally. Powers (who has left the FDA since writing his contribution) has witnessed many changes in the pharmaceutical industry in terms of the drugs being developed, as well as being responsible for introducing new scientific approaches to strengthen the regulatory process.

One key aspect he focused on is: what is antibiotic resistance? How do we define it and if it is so common why is it difficult to find and treat? Are laboratory-based resistance criteria creating hurdles that are too difficult to surmount or are we using the wrong criteria to examine the effectiveness of new drugs? Clearly, in many of the infections tested, such as exacerbations of chronic bronchitis, the endpoints evaluated may be inappropriate. Should we be looking at more patient-centric outcomes that clearly affect the patient’s life, such as the ability to climb stairs or return to work, etc, compared with assessing a clinical cure 7–10 days after the end of therapy?

Powers describes a series of trial guidelines for modern drug development. However, in relation to antibacterials the main concern is that these guidelines are applied consistently, and that the agency informs the study designers of any change in the conditions for drug approval before the drug is submitted. For several years the IDSA and others have urged the FDA to publish adequate industry guidance for anti-infective development but this document is yet to appear. Of concern in the absence of published guidelines, is whether non-inferiority trials are still acceptable to show the safety and effectiveness of a drug. Although industry is under the impression that they are still adequate, the FDA thinks otherwise.

In fairness, as concerns about the feasibility of developing new antibiotics are raised, the FDA can only approve drug-dossiers that are submitted to them, and it is clear from the diminishing number of drugs under investigation that fewer resources are being invested into antibiotic development compared with cardiovascular or other chronic medications.

There are almost 30 agents at some stage of research and development. Although a few of these will not reach phase II or III, the research initiatives described above allied with new governmental and societal efforts should help keep the antibacterial pipeline from drying up. Other stakeholders also need to be involved including patients,
health-care providers, various disease-related advocacy groups, and company shareholders. Unlike developing a new statin, β blocker, or diabetes agent, the development of a new antibacterial is a unique undertaking because antibiotics are directed at organisms that have the ability to mutate and negate our best research efforts. Only working together will we ensure the good work is not undone.

Conflicts of interest
I am an employee of Replidyne Inc.

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References
7 Kollef MH. Treatment of ventilator-associated pneumonia: get it right from the start. Crit Care Med 2003; 31: 969–70.