Novel Approaches Are Needed to Develop Tomorrow's Antibacterial Therapies

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Abstract

Society faces a crisis of rising antibiotic resistance even as the pipeline of new antibiotics has been drying up. Antibiotics are a public trust; every individual's use of antibiotics affects their efficacy for everyone else. As such, responses to the antibiotic crisis must take a societal perspective. The market failure of antibiotics is due to a combination of scientific challenges to discovering and developing new antibiotics, unfavorable economics, and a hostile regulatory environment. Scientific solutions include changing the way we screen for new antibiotics. More transformationally, developing new treatments that seek to disarm pathogens without killing them, or that modulate the host inflammatory response to infection, will reduce selective pressure and hence minimize resistance emergence. Economic transformation will require new business models to support antibiotic development. Finally, regulatory reform is needed so that clinical development programs are feasible, rigorous, and clinically relevant. Pulmonary and critical care specialists can have tremendous impact on the continued availability of effective antibiotics. Encouraging use of molecular diagnostic tests to allow pathogen-targeted, narrow-spectrum antibiotic therapy, using short rather than unnecessarily long course therapy, reducing inappropriate antibiotic use for probable viral infections, and reducing infection rates will help preserve the antibiotics we have for future generations.

Keywords: antibiotics; antibiotic resistance; market failure; drug; regulations

Antibiotics are among the most life-saving interventions in all of medicine. The absolute reductions in death mediated by antibiotics when used to treat life-threatening infections are enormous. For example, the availability of effective antibiotic therapy resulted in an approximately 25% absolute reduction in death for all comers with community-acquired pneumonia (CAP), and a greater than 40% absolute reduction in death for patients over the age of 60 with CAP (1). Similarly, antibiotics mediated absolute reductions in mortality of more than 30% for nosocomial pneumonia, 75% for endocarditis, 60% for meningeal or cerebral infections, and 11% for cellulitis (2).

Unfortunately, microbial adaptation to the selective pressure resulting from antibiotic use has inevitably led to rising rates of antibiotic resistance. At the same time, regulatory approval of new antibiotics has declined by 90% over the last 30 years in the United States (3, 4). As a result, we have fallen behind the microbes. Indeed, a national survey of infectious disease specialists found that 60% of those surveyed had encountered a pan-resistant bacterial infection, resistant to all approved systemic antibiotics, within the previous year (5).

Emerging antibiotic resistance and the faltering antibiotic pipeline are of great concern specifically for the pulmonary and critical care community. Pneumonia is one of the most common types of infection with resistant and extremely drug-resistant (XDR) pathogens. Ineffective empirical therapy often results in intensive care unit admission for sepsis and multiorgan system failure for resistant pathogens infecting other sites as well.

Obviously, we need to change direction, and urgently. A number of solutions have been suggested, and all agree that the main issues are better incentives for new drug development, reduced unnecessary antibiotic use, and improved infection prevention (6–8). This review was being written at the time that the President of the United States' Antibiotic Resistance Plan (9) was released. We have not included

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relevant facets of the plan here because of lack of clarity about its implementation, timeline, and funding.

Why Has New Antibiotic Development Declined?

There are three primary causes of the "market failure" of antibiotics (Table 1). First, after developing more than 140 antibiotics worldwide over the past 80 years, there are scientific challenges to the discovery and development of new agents (10). The low-hanging fruit has been plucked. We will need to be creative to think of new ways to screen for new antibiotics. We also must consider reducing the burden on antibiotics by considering innovative ways to treat infections that do not rely on small-molecule poisons to kill microbes.

Second, compared with other classes of drugs, antibiotics are economically unattractive for investment in research and development (R&D). Antibiotics are short-course therapies that cure their target diseases. Companies have come to realize that they can make more money selling drugs for chronic diseases that are taken every day for the rest of a patient's life (e.g., for hypertension, cholesterol, etc.). In addition, antibiotics are priced lower than other life-saving drugs (e.g., cancer therapeutics). When new antibiotics are approved, appropriate application of antibiotic stewardship principles requires us to try to minimize use of the new agents, which negatively affects sales of the drugs. The cumulative effect of these and other economic factors is underscored by a study from the London School of Economics: using a sophisticated economic model, the authors estimated that, at discovery, the net present value to a company of a new intravenous antibiotic was *minus* $50 million (11).

Third, for more than a decade, the U.S. Food and Drug Administration, particularly the Office of Antimicrobials, has been reconsidering how clinical trials of new antibiotics should be conducted (2, 4, 12, 13). This rethink was initially based on legitimate scientific and statistical concerns regarding traditional noninferiority clinical trial designs. However, the concerns have been driven to irrational extremes based solely on statistical considerations, at the expense of feasibility of trial conduct and clinical relevance of studies (13, 14). An example of the problematic approaches seen over the last decade is the serious consideration, which took more than 1 year to resolve, that placebo-controlled trials might be required to study new antibiotics to treat CAP (1, 15). Enrollment criteria, requirements regarding microbiological confirmation of the etiologic pathogen, noninferiority margin sizes, and other trial design elements have been under nearly constant reconsideration. As a result, clinical trials of new antibiotics have become far more expensive and time-consuming, and with greater risk of failing to result in approval of the experimental antibiotic, than in prior years.

The cumulative effect of increasing scientific challenges to discover new antibiotics, inadequate return on R&D investment, and increased expense and risk of clinical trials of antibiotics has been to cause numerous companies to exit the space and the pipeline to dry up.

What Can Be Done to Stimulate New Development of Antibacterial Therapies?

Overcoming Scientific Challenges

For several decades, traditional antibiotic-screening methodologies have identified the

Table 1. Causes of and Solutions to Antibiotic Resistance Crisis

Problem	Causes	Potential Solutions
Difficulty discovering new classes of antibiotics	• Easy to discover antibiotics already discovered	• Find new substrate to screen for new antibiotics • Change the screening methodology • Consider developing treatments that don't seek to kill microbes
Economically unattractive to discover and develop new antibiotics	• Companies make more money selling chronic therapies • Antibiotic pricing does not reflect societal value • Stewardship reduces sales of new antibiotics	• New business models for antibiotic development—defense contractor model • Public–private partnerships focused on new antibiotic development • Focus on developing antibiotics for resistant pathogens and unmet need, which will support higher pricing
Regulatory barriers to developing new antibiotics	• Overemphasis on exaggerated statistical concerns outweighing clinical reality and practicality in trial designs	• Regulatory reform so that regulatory standards are rigorous, but also feasible and clinically relevant
Overuse of antibiotics	• Inadequate diagnostics • Treatment regimens are too long for most infections • Continue to treat viral infections with antibiotics	• Encourage development and use of molecular diagnostics to enable targeting antibiotics and withholding antibiotics from viral infections • More studies on short-course therapy; encouraging short-course therapies clinically; biomarkers to individualize duration of therapy • Novel psychological approaches to overuse, including the "gentle nudge" approach of public commitment • Enhanced infection prevention

same candidate antibiotics over and over. New candidates have not been emerging. As we have discussed in detail in other settings, screening methodologies can be changed in two fundamental ways: (*1*) change the substrate of the screens; and (*2*) change the methodology of the screens (2, 16). Intensive scientific inquiry is needed along both avenues to discover novel antibiotic scaffolds (Table 1).

An even more transformative approach is to change fundamentally the way we think of disease, recognizing that a substantial proportion of signs and symptoms of infection are due to the host response to the infecting pathogen. Thus, it should be possible to treat infections by preventing microbes from triggering disease without trying to kill them, and/or by ameliorating the inflammatory/host response (6, 17). For example, treatment of *Acinetobacter baumannii* bacteremic sepsis with a novel experimental antibiotic that blocks the rate-limiting step of LPS biosynthesis did not kill the bacteria, but successfully rendered the viable bacteria incapable of causing disease in mice (18). Methods to treat infections that do not seek to kill pathogens should exert minimal selective pressure to drive resistance, in contrast to traditional antibiotic approaches that work by killing microbes (6).

The importance of this approach is underscored by emerging data on the normal lung microbiome (19). In contrast to previous dogma that the lung is normally sterile below the bronchi, studies have suggested that the lung microbiome reflects a continuum of microbial life from the nares to the alveoli (20, 21). The dominant organisms may be bacteria that cannot be cultured by typical methods. So, the concept that antibiotics resterilize the lung in pneumonia is no longer tenable and the off-target effects of antibiotics are just as pertinent for the lung microbiome as for the gastrointestinal tract. Changes in the continuum of flora may trigger both upper and lower respiratory tract infectious syndromes. Unfortunately, lung microbiome research is in its infancy. We do not yet have tools or knowledge regarding how to intervene or interact favorably with the lung microbiome. This is an important area for future research.

The other emerging strategy concerns the development of pathogen-focused antibiotics that may act only on a single pathogen. Even penicillin, currently thought to be narrow in spectrum, has significant effects on the primarily streptococcal and anaerobic microbiome of the respiratory (and gastrointestinal) tract. The coemergence of new non–culture-based rapid diagnostic testing makes pathogen-focused therapy a potentially feasible strategy.

Entirely New Economic Models Are Needed

The traditional entrepreneurial business model, which has been the basis of pharmaceutical R&D across all drug classes for more than 100 years, is failing antibiotics. Pharmaceutical companies traditionally expect to take all the up-front risk and pay the full costs of R&D for drugs. In return they have expected high profit margins and complete control over what drugs are developed, to enable them to bear the high up-front risk and cost.

However, in contrast to other classes of drugs, antibiotics are a "public trust." Only antimicrobial agents suffer from transmissible loss of efficacy over time caused by resistance. Indeed, antimicrobial agents are the only drugs for which use by one person affects the ability of everyone else to benefit from the drugs, due to transmissible resistance. The entrepreneurial business model encourages companies to market drugs postapproval as much as possible to maximize sales. This business model therefore encourages overuse of the precious, community property represented by effective antibiotics.

As well, companies may seek to develop new antibiotics not on the basis of unmet need but rather on risk tolerance of the clinical development program. For example, five of the six new antibiotics approved in the United States since 2008 were developed to treat skin infections caused by methicillin-resistant *Staphylococcus aureus*, even though there is no need for new agents in this space. Nor does the entrepreneurial business model prioritize drugs that have a specific unmet need if the economics of the drugs are less competitive compared with other classes of drugs. Negative net present value estimates are not compatible with entrepreneurial development.

A new business model is needed, likely a defense contractor model (Table 1). The defense contractor model enables government to help defray up-front risk and cost of R&D for products that are unlikely to be developed without financial incentives. In return for providing "push" economic incentives to defray up-front R&D risk and cost, the funding agencies gain a say in deciding which technology to develop, based on unmet public need. The funding agencies also help determine how the technology will be deployed once it becomes available. For example, defense contractors have their priorities for R&D set, their R&D costs partially covered, and their markets defined by the military and other government agencies. It might be useful to consider applying this model to new treatments for infections.

A concern about government providing funding as "push" incentives to encourage new antibiotic development is the cost of such programs. However, because of accumulated risk of failure over time of the lead candidate drug, and inflation, economic modeling has demonstrated that "push" incentives are far more efficient and less expensive than "pull" incentives (22). Pull incentives do not begin to benefit the company until after a drug is approved (22). Examples of pull incentives include lengthening marketing exclusivity, prizes, and guaranteed markets. Revenue streams from pull incentives kick in many years after discovery of a compound, and as a result, they are subject to far more value erosion due to cumulative risk and inflation. Hence, government-supported pull incentives require much larger dollar input to achieve the same impact. Push incentives are therefore more cost-effective and efficient.

A primary means to effect a change to a defense contractor model for new treatments for infection is the use of public–private partnerships (PPPs). We have discussed models and implementation options for PPP structures and functions in other settings (2, 7, 13). Government PPP programs already exist that focus on antibiotics, principally in the United States through the Biodefense Advanced Research and Development Agency (BARDA) and National Institutes of Allergy and Infectious Diseases (NIAID) in the U.S. Department of Health and Human Services, and to some extent in several agencies within the U.S. Department of Defense. In Europe, PPPs focusing on new treatments for infections are available through the Innovative Medicines Initiative (IMI) New Drugs for Bad Bugs (ND4BB) program. PPPs will

help move the paradigm toward a defense contractor model. They will help ensure that molecules are developed that address unmet needs, and that the molecules are not misused or overused postapproval.

Regulatory Reform Is Also Needed

Clinical trials for new antibiotics must be feasible to conduct, scientifically rigorous, and clinically relevant (Table 1). At present, they do not meet these requirements in the United States. Substantial reform is needed. In Europe, clinical trial guidelines for new antibiotics have been practical and relevant (23, 24). In contrast, progress has been limited in the United States. If we fix the economics but do not reform regulatory standards, the pipeline will remain inadequate.

Society needs companies to focus on developing antibiotics that meet unmet needs. Several ideas have been described for new regulatory paradigms that focus on unmet need, including the Limited Population Antibacterial Drug (LPAD) pathway proposed by the Infectious Diseases Society of America (25). LPAD trials would focus on highly resistant pathogens, enabling more rapid and smaller clinical trials, but be restricted by a narrow label, preventing marketing for broad indications that drive overuse. This idea is similar to and aligned with tier C of the four-tiered approach to antibiotic development proposed by Pharmaceutical Research and Manufacturers of America, the pharmaceutical trade organization (26). It is time to focus on developing therapies targeting infections caused by highly resistant pathogens. Crowded entry indications, such as skin infections and CAP, have become commodities markets, with numerous competitor antibiotics already available, driving down pricing and creating (appropriately) a minimal risk tolerance threshold at the regulatory level. Trials must focus instead on XDR bacterial pathogens, for which limited available therapy exists.

What Are the Implications of the Antibiotic Crisis for Pulmonary Physicians?

The major strategies to address the antibiotic crisis are new antibiotic development and improved use of currently available antibiotics. Although many pulmonary and critical care physicians remain active in the clinical evaluation of new agents, careful use of antibiotics to preserve their useful lives will be the main contribution for most. Pathogen-directed therapy with care to avoid unnecessary use is critical whenever possible. Some actions that pulmonary and critical care physicians can take to drive this agenda are described in the following sections.

Use of the New Molecular Tests for Pathogen Detection

New molecular diagnostic tests are evolving rapidly and promise to revolutionize contemporary clinical microbiology by facilitating pathogen recognition in a fashion that is both rapid and extremely sensitive. Most current attention is focused on rapid identification and antibiotic susceptibility testing of positive blood cultures, or viral detection in naso- and oropharyngeal swabs, where molecular technology is already the standard. One example is a respiratory film array panel that detects 17 respiratory tract viral pathogens and 3 bacterial pathogens in less than 2 hours. *Streptococcus pneumoniae* is in the panel, but is not approved for laboratory reporting because of concern for high rates of false positives due to respiratory tract carriage (8). This problem potentially may be overcome with a semiquantitative analysis to reduce the noise of false positives, as has been reported in prior studies from the Netherlands (19) and Finland (27). The disadvantages of this technology should also be acknowledged, and include contamination by upper respiratory tract colonization, lack of antibiotic sensitivity test results, and cost.

Ultimately, new strategies for evaluation of diagnostic tests are also needed with emphasis on clinical implications of test results, rather than simply correlation with other diagnostic laboratory tests. A positive respiratory panel for a viral pathogen other than influenza currently has no clinical significance unless clinicians are willing to discontinue antibiotics. The critical unmet need is for rapid diagnostic tests for the presence of pathogens and resistance determinants. Without these tests, clinical trials focusing on XDR pathogens will remain difficult, if not impossible. In addition, empirical clinical use of new, narrower spectrum antibiotics is untenable without a rapid diagnostic test. Although use of a new agent as "salvage therapy" once the culture diagnosis is made is preferable to the current situation, delayed use would go against the large accumulation of data on the benefit of early appropriate antibiotic therapy (27, 28). These diagnostic tests will have to be accurate in primary samples, for example, blood or bronchoalveolar lavage fluid, rather than awaiting culture growth. The silver lining of the current antibiotic resistance crisis is a reinvigoration of interest in rapid diagnostic testing.

Short-Course Regimens

Short-course regimens help reduce antibiotic use, preserving their effectiveness. Virtually every clinical trial ever conducted comparing short- versus long-course antibiotic therapy for infections has found short-course therapy to be equally effective (7). In terms of respiratory tract infections, for CAP, short-course regimens of 5 days, or even 3 days, have been as effective in large trials compared with the more traditional (and guideline-driven) use of longer courses for 7 or 8 days. Similarly, for ventilator-associated pneumonia and pyelonephritis, 8 and 7 days, respectively, have been as effective as 15 and 14 days, respectively. Withdrawal of antibiotics in culture-negative suspected ventilator-associated pneumonia has been demonstrated to be safe, as well as decreasing the subsequent development of infections with multidrug-resistant pathogens (28, 29). We are overtreating even confirmed infections, which underscores the severity of our overuse of antibiotics.

Biomarkers to Reduce Antibiotic Use

Procalcitonin is a host biomarker of activated innate immunity due to bacterial invasion that is useful in antibiotic use decision making (28, 29). The serum procalcitonin level can help decide whether an identified bacterial pathogen is colonizing or invading. A low procalcitonin level strongly supports a judgment that no bacterial pathogen is present, or if present, the bacterial organism is colonizing and not invading tissue. Normalization of procalcitonin levels can also guide duration of antibacterial therapy. In a review of more than 4,000 cases of respiratory infections in rigorously controlled trials, treatment duration guided by procalcitonin levels was on average 3.5 days shorter than in control

patients for whom procalcitonin levels were not measured, with equivalent clinical outcomes (30). As possibly expected, procalcitonin had little effect on the decision to start antibiotics in patients with CAP or nosocomial pneumonia, but subsequent reports of normal procalcitonin levels had a significant impact on stopping antibiotics earlier. The procalcitonin impact on starting antibiotics was most profound in patients with bronchitis, exacerbations of chronic bronchitis, and upper respiratory infections.

Misuse of Antibiotics for Viral Respiratory Infections

Perhaps the greatest abuse of antibiotics is with viral respiratory infections. The impressive Spanish study by Llor and colleagues confirms that antibiotics are unnecessary, and in fact potentially harmful (31). Patients with acute cough productive of discolored sputum and chest symptoms (wheezing, dyspnea, and/or pleuritic chest pain) were randomized to ibuprofen, amoxicillin-clavulanate, or placebo. The best outcome in terms of time to recover and adverse reactions was with ibuprofen. Another controlled trial for patients with "the acute cough syndrome" done in 12 European countries with 1,023 participants showed no advantage of amoxicillin over placebo (32). We have known for decades that we overuse antibiotics in patients who are highly unlikely to have bacterial respiratory infections.

Continued efforts to reduce inappropriate antibiotic use in this space are needed. For example, the "gentle nudge" (33) or "judo-like" (34) approach, consisting of a public commitment by physicians that they would not prescribe antibiotics for a viral infection, reduced antibiotic prescriptions in the outpatient setting by 20% at no cost. This approach should be adopted, and research into other psychological approaches to overcoming inappropriate prescriptions is warranted.

Prevention of Infections

Perhaps the best way to reduce the need for antibiotics is to prevent bacterial infections from happening in the first place. Examples include vaccination (e.g., Prevnar 13 for children and more recently for adults over 65 years old [35], and influenza vaccine), and efforts to prevent health care–associated infections. Prevention of ventilator-associated pneumonia now has a high national priority based on CMS data showing high mortality rates and cost estimated at more than $3 billion/year in the United States (36).

Collectively, these recommendations should make a substantial impact on the current unnecessary use of antibiotics that accounts for the acceleration of this problem.

Conclusions

We have a crisis of antibiotic resistance that is not slowing down. New approaches to overcoming scientific, economic, and regulatory barriers are needed if we are to catch up with microbial resistance. The alternative is to accept a world with rapid loss of efficacy of antibiotics, and an increasing return to the preantibiotic era for invasive and lethal infections. ■

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References

1. Spellberg B, Talbot GH, Brass EP, Bradley JS, Boucher HW, Gilbert DN; Infectious Diseases Society of America (IDSA). Position paper: recommended design features of future clinical trials of antibacterial agents for community-acquired pneumonia. *Clin Infect Dis* 2008;47: S249–S265.
2. Spellberg B, Blaser M, Guidos RJ, Boucher HW, Bradley JS, Eisenstein BI, Gerding D, Lynfield R, Reller LB, Rex J, *et al*.; Infectious Diseases Society of America (IDSA). Combating antimicrobial resistance: policy recommendations to save lives. *Clin Infect Dis* 2011; 52:S397–S428.
3. Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, Bartlett JG, Edwards J Jr; Infectious Diseases Society of America (IDSA). The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clin Infect Dis* 2008;46:155–164.
4. Shlaes DM, Sahm D, Opiela C, Spellberg B. The FDA reboot of antibiotic development. *Antimicrob Agents Chemother* 2013;57:4605–4607.
5. Hersh AL, Newland JG, Beekmann SE, Polgreen PM, Gilbert DN. Unmet medical need in infectious diseases. *Clin Infect Dis* 2012;54: 1677–1678.
6. Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotics and resistance. *N Engl J Med* 2013;368:299–302.
7. Bartlett JG, Gilbert DN, Spellberg B. Seven ways to preserve the miracle of antibiotics. *Clin Infect Dis* 2013;56:1445–1450.
8. Nathan C, Cars O. Antibiotic resistance—problems, progress, and prospects. *N Engl J Med* 2014;371:1761–1763.
9. Executive Office of the President, President's Council of Advisors on Science and Technology. Report to the President on combating antibiotic resistance. 2014 Sept [accessed 2014 Dec 24]. Available from: http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf
10. Spellberg B. Rising plague: the global threat from deadly bacteria and our dwindling arsenal to fight them. New York: Prometheus Press; 2009.
11. Sharma P, Towse A. New drugs to tackle antimicrobial resistance: analysis of EU policy options. London: Office of Health Economics; 2011.
12. Shlaes DM, Moellering RC Jr. The United States Food and Drug Administration and the end of antibiotics. *Clin Infect Dis* 2002;34:420–422.
13. Spellberg B. The antibacterial pipeline: Why is it drying up, and what must be done about it? In: Choffnes ER, Relman DA, Mack A, editors. Antibiotic resistance: implications for global health and novel intervention strategies: workshop summary for the Institute of Medicine, forum on antimicrobial threats. Washington, DC: National Academies Press; 2010. pp. 299–332.
14. Echols RM. A long and winding road; evolution of antimicrobial drug development—crisis management. *Expert Rev Anti Infect Ther* 2012; 10:1311–1319.
15. Spellberg B, Lewis RJ, Boucher HW, Brass EP. Design of clinical trials of antibacterial agents for community-acquired bacterial pneumonia. *Clin Investig (Lond)* 2011;1:19–32.
16. Fahnoe KC, Flanagan ME, Gibson G, Shanmugasundaram V, Che Y, Tomaras AP. Non-traditional antibacterial screening approaches for the identification of novel inhibitors of the glyoxylate shunt in gram-negative pathogens. *PLoS One* 2012;7:e51732.
17. Casadevall A, Pirofski LA. The damage–response framework of microbial pathogenesis. *Nat Rev Microbiol* 2003;1:17–24.
18. Lin L, Tan B, Pantapalangkoor P, Ho T, Baquir B, Tomaras A, Montgomery JI, Reilly U, Barbacci EG, Hujer K, *et al*. Inhibition of LpxC protects mice from resistant *Acinetobacter baumannii* by modulating inflammation and enhancing phagocytosis. *MBio* 2012;3:e00312-12.
19. Charlson ES, Bittinger K, Haas AR, Fitzgerald AS, Frank I, Yadav A, Bushman FD, Collman RG. Topographical continuity of bacterial populations in the healthy human respiratory tract. *Am J Respir Crit Care Med* 2011;184:957–963.
20. Dickson RP, Erb-Downward JR, Huffnagle GB. Towards an ecology of the lung: new conceptual models of pulmonary microbiology and pneumonia pathogenesis. *Lancet Respir Med* 2014;2:238–246.
21. Dickson RP, Martinez FJ, Huffnagle GB. The role of the microbiome in exacerbations of chronic lung diseases. *Lancet* 2014;384:691–702.

22. Spellberg B, Sharma P, Rex JH. The critical impact of time discounting on economic incentives to overcome the antibiotic market failure. *Nat Rev Drug Discov* 2012;11:168.
23. Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA). Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections (cpmp/ewp/558/95 rev 2) to address indication-specific clinical data. London: EMA; 2012.
24. European Medicines Agency (EMA). Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. London: EMA; 2011.
25. Infectious Diseases Society of America. White paper: recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. *Clin Infect Dis* 2012;55:1031–1046.
26. Rex JH, Eisenstein BI, Alder J, Goldberger M, Meyer R, Dane A, Friedland I, Knirsch C, Sanhai WR, Tomayko J, *et al*. A comprehensive regulatory framework to address the unmet need for new antibacterial treatments. *Lancet Infect Dis* 2013;13:269–275.
27. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest* 2002;122:262–268.
28. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, Dodek P, Wood G, Kumar A, Simon D, *et al*.; Cooperative Antimicrobial Therapy of Septic Shock Database Research Group. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest* 2009;136:1237–1248.
29. Raman K, Nailor MD, Nicolau DP, Aslanzadeh J, Nadeau M, Kuti JL. Early antibiotic discontinuation in patients with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoscopy cultures. *Crit Care Med* 2013;41:1656–1663.
30. Shorr AF, Zilberberg MD, Micek ST, Kollef MH. Predictors of hospital mortality among septic ICU patients with *Acinetobacter* spp. bacteremia: a cohort study. *BMC Infect Dis* 2014;14:572.
31. Llor C, Moragas A, Bayona C, Morros R, Pera H, Plana-Ripoll O, Cots JM, Miravitlles M. Efficacy of anti-inflammatory or antibiotic treatment in patients with non-complicated acute bronchitis and discoloured sputum: a randomized placebo-controlled trial. *BMJ* 2013;347:f5762.
32. Little P, Stuart B, Moore M, Coenen S, Butler CC, Godycki-Cwirko M, Mierzecki A, Chlabicz S, Torres A, Almirall J, *et al*. Amoxicillin for acute lower-respiratory infection in primary care when pneumonia is not suspected: a 12-country, randomized, placebo-controlled trial. *Lancet Infect Dis* 2013;13:123–129.
33. Meeker D, Knight TK, Friedberg MW, Linder JA, Goldstein NJ, Fox CR, Rothfeld A, Diaz G, Doctor JN. Nudging guideline-concordant antibiotic prescribing: a randomized clinical trial. *JAMA Intern Med* 2014;174:425–431.
34. Spellberg B. Antibiotic judo: working gently with prescriber psychology to overcome inappropriate use. *JAMA Intern Med* 2014;174:432–433.
35. Tomczyk S, Bennett NM, Stoecker C, Gierke R, Moore MR, Whitney CG, Hadler S, Pilishvili T; Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ⩾65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2014; 63:822–825.
36. Zimlichman E, Henderson D, Tamir O, Franz C, Song P, Yamin CK, Keohane C, Denham CR, Bates DW. Health care–associated infections: a meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med* 2013;173: 2039–2046.