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Discussion Guide

Modernizing Antibacterial Drug Development and Promoting Stewardship

Introduction

Antibacterial drug resistance is a global public health threat poised to worsen due to the inappropriate use of existing drugs, coinciding with a marked decline in innovative antibacterial drug development. Patients and clinicians are increasingly confronting infections caused by pathogens resistant to all antibacterial drugs in both the inpatient¹ and outpatient² settings. In order to combat antibacterial drug resistance, a two-pronged approach is needed to stimulate the development of innovative antibacterial drugs that target the greatest public health needs and to ensure that all antibacterial products are used prudently in order to preserve their utility.

Antibacterial drug development has been slowing for decades, resulting in a weak pipeline that could leave patients and the clinical community with few treatment options for an increasing number of deadly infections caused by highly drug-resistant pathogens. Following a surge of antibacterial drug development in the decades after penicillin was discovered, economic, scientific, and regulatory challenges have turned many drug development programs in therapeutic areas that are more predictable and financially rewarding under the current drug reimbursement paradigm, such as oncology and chronic disease. Efforts to reinvigorate drug development through grants, purchasing commitments, and market and regulatory incentives³ have not yet significantly strengthened the pipeline, and additional measures may be needed to overcome barriers to drug development and direct efforts toward areas of unmet need.

Under a cooperative agreement with the U.S. Food and Drug Administration (FDA), the Engelberg Center for Health Care Reform at Brookings has convened a series of expert stakeholder workshops to address major challenges in antibacterial drug development and utilization, including funding and reimbursement issues, stewardship, clinical trial requirements and statistical issues, and regulatory approaches to balance benefit and risk for the most-at-risk patients. This workshop will build upon previous work to target two key challenges: 1) the potential of pathogen-focused drug development and regulatory paradigms to stimulate antibacterial drug research for the most serious public health threats; and 2) the importance of stewardship in the treatment of common bacterial infections in the community setting. Both approaches are needed to ensure that the scientific and clinical communities are well-positioned to meet evolving public health needs in the future.

Societal Impacts of Antibacterial Drug Resistance

According to Centers for Disease Control and Prevention (CDC) estimates, every year more than two million Americans develop illness from antibiotic-resistant infections and about 23,000 die as a result.⁴ Resistance is a concern with all pathogens, but it is particularly pressing for gram-negative bacteria since no new drug class that targets these pathogens has been developed since the 1960s.^{5,6} The gram-negative family includes drug-resistant *Neisseria gonorrhoeae*, *Shigella*, *Salmonella typhi*, and non-typhoidal *Salmonella* as well as pathogens, such as carbapenem-resistant Enterobacteriaceae (CRE), extended spectrum beta-lactamase producing Enterobacteriaceae (ESBLs), multidrug-resistant *Acinetobacter*, and *Pseudomonas aeruginosa*, that can cause serious and deadly illnesses in health care settings like hospitals and nursing homes. While there are several antibacterial drugs in phase 2 or 3 clinical trials that target highly resistant infections, many experts express concern about the slow pace of research and development efforts.⁷

In addition to harming public health, antibacterial drug resistance places a heavy burden on society due to the direct and indirect costs associated with drug-resistant infections. The direct cost incurred by the U.S. health care system on account of these infections is estimated to be over \$20 billion annually. When lost productivity is included, the total amount of excess costs related to drug-resistant infections increases to \$35 billion per year.⁸ Beyond domestic concerns, drug resistance is also a major source of morbidity, mortality, and excess health spending globally, and is projected to become a larger problem in the coming decades, particularly in the absence of concerted efforts to stimulate drug development and combat the inappropriate use of antibacterial drugs.

Challenges in Antibacterial Drug Development

Antibacterial drug development has been on a steady decline for several decades due to a number of economic, regulatory, and scientific challenges. One major economic challenge is that antibacterial drugs have historically been reimbursed at relatively low rates. Pricing for an antibacterial drug rarely exceeds \$100, even at market entry.⁹ Moreover, antibacterial drugs tend to be used as short course therapy and are curative in nature, which limits a developer's opportunity to generate significant returns. Natural selection for drug-resistant pathogens also means that antibacterial drugs will become less profitable over time, unlike products to treat other conditions such as hypertension where, although individuals may need higher doses over time, the product's efficacy is not compromised by broad use in the community. Furthermore, antibacterial stewardship programs aim to limit use of powerful new drugs to treatment of serious infections where few treatment options exist, further restricting this market.

These factors have created a difficult investment environment for pharmaceutical and biotechnology companies, many of which have dissolved or minimized their antibacterial development programs in favor of therapeutic areas with more durable and profitable markets. However, some newer antibacterial drugs have been reimbursed at much higher rates than older products¹⁰ and various stakeholders and payers agree that this pricing structure may be appropriate for drugs that treat more serious infections and provide better outcomes.¹¹

Approaches that seek to reduce development costs could also help provide a favorable balance of investments and returns. Like most drugs, antibacterial products face high development costs, particularly for late-stage clinical trials, but additional factors can complicate clinical trials in the infectious disease space. For example, patients with serious infections are likely to be acutely ill and in need of urgent therapy, which can preclude efficient consent and timely trial enrollment procedures. In addition, many patients with serious drug-resistant infections have significant comorbidities that may render them less likely to meet inclusion criteria, thus precluding study enrollment.

Uncertainty about the pathogen and the need to rapidly and empirically treat ill patients can also complicate trial recruitment for pathogen-focused drugs. Because traditional cultures may take days to identify a pathogen, it is often impossible to use narrow-spectrum drugs when initiating treatment for serious infections. Consequently, a physician might treat the infection empirically, which can confound treatment effects if the patient is later enrolled in a trial for an experimental therapy. Ultimately, uncertainty about the etiology of an infection may necessitate trials with larger numbers of patients in order to achieve sufficient statistical power after diagnoses are confirmed for the pathogen of interest. This may be logistically challenging given the nature of serious bacterial infections and the low incidence of highly resistant pathogens.

Opportunities for Modernizing Antibacterial Drug Development

FDA's goal when evaluating new therapies is to protect public health by ensuring that benefits to patients outweigh risks. FDA recognizes the need for new treatments for serious diseases with unmet medical need, as well as the challenge of real-world study feasibility in bringing these products forward in development. FDA has outlined several expedited regulatory pathways that ensure sufficient collection of clinical trial data to support an adequate benefit-risk determination and a timely approval of new products for use in those who need them most.

In the case of serious diseases with unmet medical need, the accelerated approval pathway allows for treatments to be approved on the basis of a surrogate endpoint or intermediate clinical endpoint that is

reasonably likely to predict a drug's clinical benefit.¹² The Agency, in some instances, has also approved products using data from smaller, single, or externally or historically controlled trials. Orphan drugs, for example, which treat conditions that affect fewer than 200,000 people in the U.S., have been approved on the basis of data that included very small clinical studies, single studies, case series, and historically controlled trials.¹³

Recognizing that serious bacterial infections with drug-resistant pathogens represent a significant and growing unmet medical need, drug regulatory agencies have begun exploring approaches to antibacterial drug development that support innovation in a challenging clinical space. The European Medicines Agency recently released its *Guidance on evaluation of medicinal products indicated for treatment of bacterial infections*, as well as an addendum containing information on the development of agents with a very narrow spectrum of antibacterial activity.¹⁴ FDA's *Guidance for Industry on Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases* is expected by the end of 2014; draft guidance was made available for comment in summer 2013.¹⁵

Streamlined drug development programs and more targeted regulatory requirements have been proposed to incentivize the development of antibacterial drugs that address unmet therapeutic needs. The Limited Population Antibacterial Drug pathway, which was developed by the Infectious Diseases Society of America, would restrict antibacterial drug indications to a narrow population of seriously ill patients.¹⁶ Clinical trials would be relatively small and enroll only patients with serious infections such that any known risks and risks associated with uncertainty about the drug's safety would be outweighed by the drug's benefits for this population. A drug approved through this mechanism would not be appropriate, for instance, to treat patients with less serious infections or when effective therapeutic alternatives are available. Products approved through this proposed pathway would also require stringent labeling and likely carry a special logo alerting practitioners of the need to use the product judiciously, as estimates of risk are less precise.

Other proposals similarly aim to reduce the burden, cost, and time for clinical development in order to balance benefit-risk profiles and evidentiary requirements with unmet need. A recent paper by Rex *et al.* details a tiered regulatory framework for approving antibacterial drugs, with the level of clinical evidence required correlated with the seriousness of the public health threat and the feasibility of generating clinical evidence.¹⁷ Whereas two large randomized, controlled phase 3 trials are the standard for most drug approvals (tier A), Rex *et al.* argue that when a pathogen is rare, drug approval can be supported by several small, comparative, descriptive, or possibly historically controlled trials that investigate the use of a drug in treating a specific pathogen or pathogens (tier C). If a pathogen is sufficiently rare, it may be necessary to enroll patients with infections at multiple body sites in order to generate an appropriate level of evidence, rendering a disease-based indication (e.g., acute bacterial skin and skin structure infections (ABSSSI)) inappropriate. An intermediate tier (tier B) would combine descriptive study with a single controlled trial. The narrowness of the indication would reflect the relative level of certainty about risks and the scope of the clinical evidence.

A pathogen-focused approach could be useful in targeting development toward the most serious needs (e.g., using FDA's proposed list of pathogens with the potential to pose a serious threat to public health¹⁸) and in streamlining clinical evidence generation. Targeted development programs supported by a clearly defined regulatory framework could lower barriers to clinical research, thereby stimulating investment in innovative antibacterial drugs. The scope of clinical evidence required for a pathogen-focused development program could take into account many factors, including the incidence of the infection and the ability to rapidly identify: 1) patients with the pathogen of interest; and 2) the genus, species, and susceptibility of the pathogen. Approaches could be informed by the drug's spectrum of activity, for example, against the following sets of pathogens:

- a group of related pathogens (e.g., all gram-negative);
- pathogen(s) with genes that encode a specific mechanism of resistance (e.g., OXA-type carbapenemases); or
- a specific bacterial genus, species, or strain.

As discussed above, the term "pathogen-focused" has also been used to describe clinical development programs that incorporate infections by a single pathogen at multiple body sites, in contrast to a disease-focused approach (e.g., ABSSSI). Pooling data across multiple infection types could facilitate investigations of very rare pathogens; however, this approach may not be clinically appropriate in every case.¹⁹

Additional Data Considerations in Modernizing Antibacterial Drug Development

Streamlined antibacterial drug development programs will need to balance benefits to patients with risks associated with uncertainty about the product. Where uncertainty is likely to persist due to difficulties developing large efficacy datasets, nonclinical evidence and more refined data points (e.g., biomarkers, pathogen genotypes, etc.) can potentially play a greater role in supporting drug development, approval decisions, and clinical use.

Pharmacokinetics and Pharmacodynamics

Some have suggested that pharmacokinetics and pharmacodynamics (PK/PD) data could play a larger role in the drug approval process where clinical evidence is more limited. In the antibacterials space, in particular, PK/PD data could play a larger role in identifying promising compounds and expediting clinical drug development. PK/PD data can be used to demonstrate proof of concept or mechanism prior to clinical testing, and to characterize and predict bacterial growth, inhibition, and killing in response to drug exposure.²⁰ These data can then be used to support dose optimization, reducing the need to conduct clinical evaluations of dose response. Where margins for success may be thin, the application of PK/PD principles to clearly establish proof of mechanism and dosing schedules can potentially reduce late-stage drug failures.^{21,22}

Clinical Endpoints

The lack of rigorous and objective measures to assess the effect of experimental agents has potentially contributed to regulatory uncertainty in the infectious disease space and limited opportunities for antibacterial drug development.^{23,24} While mortality is easily measured and a direct measure of clinical benefit, it is not always an ideal efficacy endpoint since mortality in patients with serious bacterial infections, who often have several comorbidities, is often not clearly attributable to therapeutic failure. Some antibacterial trials have used clinical cure measures as primary endpoints; however, such measures may be subjective and may not be predictive of all-cause mortality.²⁵ Microbiological test-of-cure data may be difficult to obtain (e.g., sputum samples following resolution of the infection) and may also not distinguish colonization from infection.²⁶

Antibacterial drug development could be supported by further development and validation of well-defined, clinically meaningful, and reliable outcomes measures that directly measure clinical benefit in terms of improvement in how patients feel, function, and survive.^{27,28} The Biomarkers Consortium of the Foundation for the National Institutes of Health recently investigated historical evidence of antibacterial treatment effects. They identified a number of putative endpoints, and found that the largest treatment effects can be documented early in the course of the disease (e.g., patients that respond to therapy are likely to respond early).²⁹ This has positive implications for the development of valid clinical endpoints. There is also a need to develop surrogate endpoints that are "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit."³⁰

Diagnostics

A major challenge for accelerating pathogen-focused drug development is the lack of pathogen-focused rapid diagnostics, particularly for gram-negative bacteria. With this in mind, the Infectious Diseases Society of America recommended that federal incentives to stimulate diagnostics research and development should be targeted toward tests that are "pathogen-specific" and linked to the pathogen's drug resistance profile.³¹ Diagnostics that rapidly identify specific bacterial pathogens and their particular mechanisms of resistance and related susceptibility profiles have the potential to improve drug development, clinical use, and stewardship efforts over the long term, benefiting a broad group of patients and health care stakeholders.

Rapid diagnostics are an essential component of streamlined clinical trials and will be critical for improving trial cost-effectiveness. Rapid and accurate point-of-care diagnostics would facilitate patient screening and enrollment for trials, and support smaller trial sizes by ensuring that a higher percentage of participants would have the pathogen of interest. Effective point-of-care diagnostic tools could also improve clinical use and stewardship efforts by allowing for targeted rather than empiric treatment. This could slow the development of resistance to other agents and prevent patients from being exposed to ineffective drugs or unnecessary drug interactions and adverse effects.^{32,33}

There has been much advancement in diagnostic technologies over the past decade. New developments such as the detection of pathogen nucleic acids and proteins have led to testing that is highly sensitive, specific, and rapid. For example, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) can identify a pathogen from clinical isolate in under an hour, whereas traditional phenotypic methods such as automated and manual panels of biochemicals require between 24 to 48 hours to identify a pathogen and to determine its susceptibility profile. The upfront costs for a MALDI-TOF MS unit are significant; however, routine testing costs are less than for traditional systems.³⁴ Ultimately, MALDI-TOF MS and other promising diagnostic technologies offer hope not only to drug developers with pathogen-focused drugs in their pipelines, but also to clinicians and patients battling multidrug-resistant pathogens in hospitals around the world.

Promoting Stewardship

In 2010, 258 million courses of antibiotics were prescribed for outpatient use in the United States; in some states prescribing exceeded the rate of one prescription per person.³⁵ Up to 75 percent of ambulatory antibiotic prescriptions are for the treatment of five acute respiratory infections³⁶ – otitis media, sinusitis, pharyngitis, bronchitis, and upper respiratory tract infections – that may or may not be bacterial in origin. About 50 percent of antibacterial drug prescriptions are thought to be inappropriate (e.g., for a viral infection).³⁷ Although antibacterial prescribing for respiratory infections has decreased overall in the last several decades,³⁸ rates of prescribing are still high, and many of these prescriptions are still likely to be unnecessary. Rates of prescribing are especially high in seniors and children,³⁹ with more than 20 percent of ambulatory pediatric visits resulting in prescriptions for antibacterial drugs.⁴⁰ Despite declines in the use of antibiotics for pharyngitis and nonspecific upper respiratory infections (common cold), rates of prescribing for otitis media, sinusitis, and bronchitis in children have shown little decrease since the mid-1990s.⁴¹

Antibacterial usage for acute respiratory infections in the ambulatory care setting is largely driven by physician and patient expectations, low costs, and a general unfamiliarity with the risks associated with antibacterial drugs. In the case where an infection is likely to be viral, physicians may prescribe antibacterial drugs in order to appease a patient and because they feel that little harm can come from the use of an antibacterial drug. Physicians may also prescribe broad-spectrum antibacterial drugs, where a more targeted drug may be more appropriate.⁴² On a public health level, these practices have contributed to the development of resistance in a number of pathogens, but the inappropriate use of antibacterial drugs also has immediate consequences for individual patients.

There are more than 140,000 emergency department visits annually for adverse events related to antibacterial drugs, most of which are allergic reactions.⁴³ In addition, antibacterial use can compromise a patient's natural balance of gut microbes by eliminating healthy bacteria. This leaves many patients vulnerable to infection with *Clostridium difficile* (*C. difficile*), which causes 250,000 infections per year requiring hospitalization or affecting already hospitalized patients.⁴⁴ These infections cost the health care system more than one billion dollars in excess medical care. *C. difficile* has become more virulent since 2000, and now causes 14,000 deaths annually. The danger this pathogen poses was recognized by the CDC in 2013 when it listed *C. difficile* as an urgent public health threat.

Changing practices and expectations around antibacterial drugs has proven to be a major challenge for common indications, including the acute respiratory infections cited above. Ill patients or their caregivers generally expect to receive medication at the end of a visit to a physician's office, and physicians often find that it's faster to prescribe a broad-spectrum antibacterial drug than to conduct a diagnostic test or explain to the patient why an antibacterial drug is likely unnecessary. These practices have been

facilitated by the relatively low cost of most antibacterial drugs. The CDC's Get Smart: Know When Antibiotics Work campaign, as well as a number of other educational efforts, has aimed to educate the general public of the fact that colds, flu, most sore throats, and bronchitis are viral in origin, meaning that antibacterial drugs are unlikely to cure the infection. The CDC has also collaborated with respiratory disease specialists to develop and promulgate guidelines that help clinicians use antibacterial drugs appropriately.⁴⁵

The broader health care system has a role to play in reducing the inappropriate use of antibacterial drugs in the ambulatory care setting. In hospitals, for instance, teams of infectious disease physicians and pharmacists work together to oversee the use of antibacterial drugs for serious infections. Hospital stewardship programs generally include preset plans and criteria for escalating or deescalating antibacterial therapy. In the ambulatory care setting, there may be less oversight and changing practices can be more challenging. However, clinical guidelines, which are typically developed by professional physician organizations, can alter practices among the wider physician community. In recent years, new guidelines^{46, 47} have sought to take more judicious and evidence-based approaches to caring for upper respiratory indications, particularly in children.⁴⁸

Clinical guidelines are often used as a basis for formulary guidelines, which indicate the products and uses of products that will be reimbursed under an insurance plan's pharmacy benefit. Pharmacy benefits managers typically review clinical evidence to set these guidelines, with the goal of shaping physician practices. By helping establish an evidence-based framework for antibacterial prescribing, payers may play a role in supporting stewardship, particularly in the ambulatory care setting. Payers, for instance, could deny coverage for antibacterial drugs to treat pharyngitis in the absence of a documented positive strep test. Though antibacterial drugs used in ambulatory care tend not to be very expensive, consumers may alter their expectations when required to pay out-of-pocket.

Workshop Objectives

This workshop is divided into two sessions to address the thin antibacterial drug development pipeline and the need to strengthen stewardship in the ambulatory setting. During the workshop's morning session, experts from the drug development and health care industries, the clinical community, government, and academia will discuss potential antibacterial drug development programs that target serious bacterial diseases. Participants will explore pathogen-focused programs, such as those that target a specific pathogen or group of pathogens, as an approach in addressing unmet need. Participants will also discuss the role of rapid diagnostics, pharmacokinetics and pharmacodynamics data, and validated clinical endpoints in supporting modernized antibacterial development programs. The afternoon session will examine approaches to combating the overuse of commonly prescribed antibacterial drugs in the ambulatory setting, with special consideration of acute respiratory infections. Participants will discuss benefit-risk considerations for drug approval, and stewardship efforts in the ambulatory setting, including the impact of guidelines, provider and patient education, and other strategies to change expectations and behaviors related to the use of antibacterial drugs.

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