

## **Proceedings**

### ***International Workshop on Antibiotic Resistance: Global Policies and Options***

***Center for International development<sup>1</sup>***

**Harvard University**

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## **Executive Summary**

The increasing failure of antibiotics to treat commonly curable infectious diseases represents one of the most significant challenges to the medical profession in modern times. This failure is caused by growing bacterial resistance to antibiotics and is a direct outcome of the selective advantage provided by the use of antibiotics to resistant bacteria. In particular, the increase in antibiotic resistance associated with hospital-acquired infections has resulted in increased morbidity and mortality, longer hospital stays and more frequent hospital and ICU readmission. Consequently, the cost of treating a drug resistant bacterial infection has been reported to be much greater than the cost of treating a susceptible infection.

Although the potential for resistance was recognized as early as in the 1940s when antibiotics were first introduced, significant increases in resistance have been noted only in the last two decades. The problem has been exacerbated by the absence of new antibiotics over this time period. In fact, the last major antibiotic class to be discovered, carbapenems, was first identified nearly two decades ago.

It is frequently recognized that the widespread use of antibiotics, both in medicine and agriculture, represents an important reason for the increase in antibiotic resistance. Also contributing to the problem is sub-therapeutic use of antibiotics and the failure of patients to complete a full course of antibiotic treatment in outpatient settings. Although there is consensus on the need to reduce antibiotic use, and to use them more carefully, there is less clarity on the nature of policy mechanisms that could promote judicious antibiotic use. Consequently, international efforts to tackle the antibiotic resistance have been slow to emerge and are for the most part, restricted to surveillance of antibiotic resistance.

From an economic perspective, the antibiotic resistance problem arises from the absence of incentives for individuals to take into account the negative impact of their use of antibiotics on social welfare. Therefore any solution to the problem of antibiotic resistance requires not only that it be medically sound, but also that it be aligned with incentives faced by patients, doctors, pharmaceutical firms, and public health regulatory agencies. To this end, an interdisciplinary workshop was organized to identify topics for a multi-disciplinary research agenda to tackle the global problem of antibiotic resistance. Conference participants included physicians, epidemiologists, economists, sociologists, legal professionals, and policy makers.

The workshop was organized into three sessions. The first session addressed issues related to optimal antibiotic use in hospital settings. Specifically, the session featured natural resource economics research as an analytical framework in which study optimal cycling strategies.

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<sup>1</sup> This report was prepared by Julia Aledort, Ramanan Laxminarayan (Workshop Organizer), David Howard and Erica Seiguer. Additional assistance was provided by Susanne Weldon. More information and background material on the conference are available at <http://www.cid.harvard.edu/cidabx/> Please forward comments to [ramanan@rff.org](mailto:ramanan@rff.org)

Issues related to the role of the pharmaceutical industry were addressed in the second session. These issues relate mostly to incentives to pharmaceutical firms in discovering and developing new antibiotics and the role of patents in influencing these incentives. The case of antibiotics is complicated by two factors. On the one hand, firms may have an incentive to care about resistance as long as the antibiotic is under patent protection. On the other hand, lower resistance to an existing antibiotic in the firm's portfolio of drugs implies reduced returns to any investment that the firm may be making in a new antibiotic. Work presented in this session examined the impact of intellectual property rights in discouraging the development of diversified portfolio of antibiotics over the product space, and discussed incentives that could be provided to manufacturers to increase research spending on new antibiotics.

The third session was devoted to institutional issues such as surveillance, legal aspects of antibiotic resistance, and regulation of new antibiotics. In recent years, there has been greater emphasis on antibiotic surveillance both to gather information about the impact of antibiotic use on resistance, as well as to inform public health and hospital decision-makers about the development of resistance. One of the largest of these surveillance systems, WHONET, gathers information at a global level. The economic importance of these surveillance systems and the value of the information collected were subjects of discussion. The session also featured presentations on the legal issues of antibiotic resistance as a global public externality, in much the same way as trans-boundary pollution issues, and on the usefulness of labeling for antibiotic resistance in encouraging judicious antibiotic use.

The workshop concluded with a panel discussion to identify areas for future multidisciplinary research between those in the medical and public health fields, and social scientists. Since the problem of antibiotic resistance is in many respects a behavioral problem related to the lack of incentives for physicians and patients to internalize the impact of their antibiotic use decisions on society, there is scope for application of economic tools to study these incentives. The panel, which was composed of two public health policy makers and an economist, examined key issues related to antibiotic resistance, especially in the context of the developing world. Examples include role of medication costs in preventing patients from completing a full antibiotic regimen, and the link between physicians' salaries in some countries, and the over-prescription of antibiotics.

The workshop was successful in bringing to bear diverse skills and opinions on the problem of antibiotic resistance. A number of important topics were debated related to physician prescribing behavior, optimal antibiotic use patterns in hospital settings, and incentives faced by drug firms to engage in new drug discovery investment. The workshop also addressed issues of antibiotic resistance in the context of the developing world, where its impact is likely to be the most severe. The workshop highlighted the substantial and multidisciplinary research effort required to understand the behavior of patients, physicians, hospitals, and the pharmaceutical industry with respect to resistance, and of formulating economic solutions to this time-critical problem.

### **Opening Remarks**

*Jeffrey Sachs, Ph.D., Center for International Development, Harvard University*

Dr. Sachs opened the conference by describing how development economists and agencies, once focused on traditional "macro" issues such as exchange rates and budget deficits, are increasingly recognizing the importance of health in development. Recently, the World Health Organization (WHO) established the Commission on Macroeconomics and Health, of which Dr. Sachs is the Chair, to examine

- The relationship between poor health and poverty;
- The role of governments in establishing incentives for research and development of drugs to treat diseases prevalent in developing countries, and;
- The scale of public health aid to developing countries.

Ongoing research on malaria has demonstrated the severe burden that disease places on poorer nations. One goal of CID is to bring together researchers from various disciplinary backgrounds to address the problem of malaria and other global health issues.

With regards to antimicrobial resistance (AMR), Dr. Sachs highlighted several areas in which researchers can contribute to policy development. First, there is no national or international framework for addressing the externalities entailed in antibiotic use as evidenced by disputes between the European Union and the United States over the use of antibiotics in animal feed. Second, there is a lack of research on the scale of AMR in non-hospital settings, which are more relevant to the developing world. Finally, there is a need to identify policy responses and the institutions responsible for carrying out those policies. In this context, questions such as ‘where are the highest priorities for policy response?’ and ‘who will be the central actors?’ have to be addressed seriously.

### **Session I: Optimal Antibiotic Use**

#### ***“The Epidemiology of Antibiotic Resistance in Hospitals: Paradoxes and Prescriptions”***

***Mark Lipsitch, D. Phil., Department of Epidemiology, Harvard School of Public Health***

Evaluations of interventions to reduce AMR in the medical literature show that:

1. The lag between program initiation and AMR reduction varies depending on setting (i.e. hospital or community),
2. Interventions targeted at both resistant and non-resistant bacteria are effective in reducing AMR,
3. The use of one antibiotic is a risk factor for carrying bacteria resistant to another.

Dr. Lipsitch presented an epidemiological model that formalizes these results and can be used to calculate appropriate timeframes and outcome measures for future studies. In the model, individuals enter the hospital colonized with resistant or sensitive bacteria or bacteria-free but subject to infection. Patients are treated with one of two drugs (treatment rates are assumed exogenous). The first drug is effective in treating only sensitive patients. The second, which acts as a proxy for broad-based interventions, is effective in treating all infections. The model predicts that non-specific interventions (represented by drug two) and switching will disproportionately reduce the prevalence of resistant bacteria and that the reduction will take place in a short timeframe. The key feature of the model driving this result is that bacteria are constantly introduced into the hospital by newly admitted patients. When the resistant bacteria are successfully treated, the sensitive bacteria will “wash-out” the resistant bacteria. Dr. Lipsitch also noted that increased use of the effective drug (drug two) reduces the prevalence of resistant bacteria while increasing the odds that patients treated with the effective drug carry the resistant bacteria.

Dr. Lipsitch made three concluding points:

- Models can be useful in explaining empirical findings on the responsiveness of resistant bacteria to interventions and estimating the lag between an intervention and the decline of resistant bacteria.

- Investigators should be sensitive to the divergence between individual versus population measures of AMR when evaluating study endpoints.
- Simply reducing use of an antibiotic may be less effective in reducing the prevalence of AMR than switching to a more effective drug.

***“The Economics of Cycling Antibiotics”***

***Dr. Ramanan Laxminarayan, Ph.D. Resources for the Future***

Dr. Laxminarayan began by stressing the applicability of existing economic models of natural resource use to the problem of AMR. Furthermore, he emphasized the importance of balancing conservation of antibiotic effectiveness for the future against the objective of curing disease in the present.

Previous literature on antibiotic use has recommended that hospitals use two or more antibiotics simultaneously, based on purely biological factors. Consideration of the fixed costs of maintaining an antibiotic on formulary and the cost of switching between antibiotics reverses this result: in the presence of these costs, hospitals should switch from one antibiotic to the other and back again. This result parallels findings in models of inventory control and tree-harvesting. Dr. Laxminarayan also pointed out that resistance follows a logistic curve so that use of antibiotics affects resistance in a non-linear fashion. This explains why many hospitals face low levels of resistance for long periods of time before experiencing sharp increases in resistance relatively quickly.

Numerical analysis of the model using time series data from a large hospital demonstrates the relationship between the optimal cycling time and a number of key parameters. For example, the length of the period between switching from one antibiotic to the other, is negatively related to the fitness cost (the rate at which resistant strains die out naturally, in the absence of ineffective antibiotic use). However, cycling can be beneficial even when the fitness cost is zero, as long as the hospital faces a cost of storing an antibiotic on the formulary, and of switching from one antibiotic to another.

***“Nomenclature and Methods for Studies of Antibiotic Switching (cycling)”***

***Carl Bergstrom, Ph.D., Department of Biology, Emory University***

Dr. Bergstrom continued the discussion of cycling by pointing out that there are two types of cycling policies. Proactive switching is changing from one antibiotic to another on a preset schedule. Reactive switching occurs when hospitals change from one antibiotic to another depending on the level of resistance at a particular point in time. He defined the level of resistance at which switching occurs as the “trigger.” The effectiveness of reactive switching can be evaluated by comparing the incidence and prevalence of AMR under switching to the outcomes under the status quo or under an aggressive infection control policy. Empirical evidence on reactive switching generally confirms theoretical predictions; reactive switching produces results quickly, is effective when resistance is rare in the community, and is more effective than simply reducing antibiotic use.

Proactive switching is designed to prevent the development of AMR and bring about a reduction in the incidence of resistance. Empirical evidence is limited, but the experience of switching in one cardiac surgery unit suggests that it is an effective means of lowering infection and mortality rates. In contrast, epidemiological models suggest that proactive cycling is not likely to be effective in the community setting and likely to be effective in the hospital *only* if resistance is eradicated entirely for a period of time. Heterogeneous assignment of patients to drugs may be a more promising alternative.

Questions for future research include:

- How does the effectiveness of reactive switching vary with the degree of resistance, the level of compliance, and other variables?
- How quickly does reactive switching eliminate resistance and when can the original drug be restored?
- How should optimal proactive switching protocols be designed and under what conditions are they likely to be effective?
- How do proactive switching policies affect the path of AMR?

***“Issues Concerning Studies on the Impact of Health Care Associated Infections with Antibiotic Resistant Pathogens”***

***Ralph Cordell, Ph.D., Hospital Infections Program, Centers for Disease Control and Prevention***

Dr. Cordell began with an overview of data collection, study design, and cost and patient outcome measures in the evaluation of AMR-related interventions. As with all clinical studies, the cost and degree of difficulty of data collection depend on study endpoints. Lengths of stay data are relatively easy to collect within a single institution. Trained reviewers must collect data from medical records for more detailed endpoints such as appropriateness of care or costs attributable to infections.

Obtaining adequate controls for AMR cohort studies presents a challenge. Typically infected cases are matched to controls (uninfected or infected with sensitive bacteria) on observable characteristics such as severity of underlying illness. The more detailed are the observable characteristics used to match cases and controls, the larger must be the underlying patient population from which controls are drawn. Researchers, therefore, face a tradeoff between sample size and internal validity.

Cost data, typically taken from hospital charges, are an important component of any economic study of AMR. Previous research indicates that resistant infections are more expensive to treat than sensitive infections, although Dr. Cordell suggested that the magnitude of the cost difference is confounded by unobservable patient characteristics (studies with better matching produce lower cost differentials). Challenges for future research include measuring costs from the societal perspective and estimating the true relationship between disease severity and the financial burden of AMR. Besides using more accurate disease severity measures, researchers may want to examine the effect of interventions on the change in health rather than simply looking at absolute levels. Another difficulty in conducting empirical research is that classification of patients into infected and resistant groups is often based on subjective physician judgements and subject to error.

Dr. Cordell concluded by discussing the Chicago Antibacterial Resistance Project (CARP) cost model currently under development. The model uses information extracted from medical and laboratory records to classify patients' infections as resistant or sensitive and applies standard disease severity measures to assess the impact of AMR on patient outcomes.

***Discussants:***

***Jim Wilen, Ph.D., University of California, Davis; Bob Rowthorn, Ph.D., University of Cambridge***

Dr. Wilen began the discussion of the first session by reiterating the applicability of many natural resource models to the problem of preserving antibiotic effectiveness. Dr. Wilen noted that economists have developed tools to measure treatment effects and costs, and that these tools may

be useful for evaluating AMR policies. Dr. Wilen concluded by discussing the usefulness of theoretical models in AMR research as evidenced by the counterintuitive results of the model presented by Dr. Lipsitch. One such result is the divergence between individual and population measures of resistance in response to interventions.

The second discussant, Dr. Rowthorn, alluding to Dr. Bergstrom's presentation, observed that if the path of disease resistance is known with certainty, there is no difference between reactive and proactive switching. Given uncertainty, however, the reactive strategy would seem to dominate proactive switching by making use of information on resistance levels.

Dr. Rowthorn commended Dr. Laxminarayan for demonstrating the impact of fixed costs on optimal antibiotic use policies, but wondered about the duration of the transition to the steady state and its policy relevance. Dr. Rowthorn highlighted the interesting result in the model of a unique coincidence between individual and social incentives at the steady state, and urged Dr. Laxminarayan to pursue this finding further.

Comments from the audience focused on the limitations of cycling models and epidemiological modeling generally. Dr. David Bell stated that cycling is but one of many policy options and is unproven. Future models should also consider more appropriate drug selection. Dr. Mac Hooton commented on the importance of considering the specific context and setting in which cycling is to be applied. Dr. Gerald Keusch pointed out the limitations of models that do not take into account factors that give rise to resistance problems and the complexity of medical decision making with respect to antibiotic prescribing.

## **Session II: Incentives for Judicious Antibiotic Use**

### ***“Lost Horizons: The Interaction of IPR Systems and Resistance Management”***

***Timo Goeschl, Ph.D., Department of Land Economy, University of Cambridge***

***Dr. Timothy Swanson, Ph.D., Faculty of Law and Department of Economics, University of London***

Following earlier literature on the economics of bacterial and pest susceptibility, Drs. Goeschl and Swanson regard the effectiveness of antibiotics as a renewable resource. In this context, a “first-best strategy for pathogen management” is seen as one in which many antibiotics would be applied to the treatment of disease while minimizing the potential for the development of resistant strains of bacteria. In this “golden age,” there would exist a sufficient number of antibiotics to keep a steady state which will not induce resistance due to the re-charge periods of antibiotics.

Drs. Goeschl and Swanson credit the failure of the first-best strategy to materialize on the current incentive system and an industrial structure that is “disaggregated across both time and space.” The incentive system consists of pharmaceutical firms producing antibiotics, with the knowledge that their ability to profit from the R&D investment is limited by the intellectual property system in the form of patents. At the same time, the industrial sector employing the antibiotics is decentralized, and the drugs are used on a case-by-case basis. This paradigm leads to

:

- The development of a small number of antibiotics;
- Extensive use of antibiotics;
- Uniform treatment portfolios across all sites, and;
- Continuing loss of effectiveness.

Drs. Goeschl and Swanson conclude that under the current IPR system, private and social incentives do not match. The current intellectual property rights system leads to the development of a diversified portfolio over *time* but not in space. Thus, a shift in the organization of institutional structures is needed in order to improve the mismatch between the solution generated by the economy, and the solution under the social optimum. They propose that in order to achieve the social optimum, governments require the development of a diversified portfolio of antibiotics used across space.

***“Incentives Faced by Drug Firms to Conserve Antibiotic Effectiveness”***

***Richard Bax, Ph.D. Transcrip Ltd., UK***

In light of increasing AMR and declining interest on the part of industry to invest in R&D for antibiotics, Dr. Bax predicted an impending “window” during which current antibiotics will have lost efficacy and no new drugs will be available. Dr. Bax’s presentation focused on the creation of incentives for the pharmaceutical industry to conserve antibiotic effectiveness and proposals from industry to improve the current situation.

Dr. Bax asserted that one of the most important components in the development of AMR is the fact that physicians generally do not perceive how their prescription patterns affect the community at large. According to Dr. Bax:

- Differences between “good” and “poor” prescribing are not apparent to individual patients and physicians,
- Results of the development of resistance are not clear, and;
- Clinical trials do not provide information on optimal antibiotic use.

Dr. Bax spoke about the lack of incentives for the pharmaceutical industry to both conserve antibiotic effectiveness and develop new antibiotics. Currently there are few incentives for industry to devote resources to the research and development of new antibiotics. While the market for antibiotics has remained relatively constant, other anti-infectives, including antivirals and antifungals, have seen an increase in market size. Moreover, antibiotics capture a much smaller share of the world market than drugs in other therapy classes. In response to these challenges, the U.S. pharmaceutical industry trade group, the Pharmaceutical Research Manufacturers of America (PhRMA), has proposed three policies to deal with AMR:

- Fund R&D on important anti-infectives through the use of tax breaks;
- Fund post-approval clinical development and microbiology studies, and;
- Grant patent extensions on non-antibiotic products to companies that develop narrow-spectrum antibiotics.

Generally the industry supports appropriate use of antibiotics and policies that increase the price per dose. Industry does not, however, support decreasing the duration of the dosing regimen, increasing the use of diagnostics, or mandating the development of narrow- versus broad-spectrum antibiotics. In this context, it has to be considered that the major antibiotic burden is not the high value, but the off-patented products.

In addition to identifying possible approaches to creating incentives for the pharmaceutical industry to become more active in the field of antibiotic research, Dr. Bax proposed the following “hot” topics in the field:

- The constraints of antibiotic use in some markets;

- The potential for the development of guidelines and computer-assisted prescribing;
- The role of vaccines in controlling the development and spread of resistance;
- The development of rapid susceptibility testing techniques;
- The development of pharmacokinetic and pharmacodynamic data for rational dosing, and;
- New emerging pathogens.

Dr. Bax concluded by stressing the need to develop models of antibiotic resistance, to investigate the spread and persistence of resistant pathogens, to clarify the strengths and weaknesses of clinical trials, and to link antibiotic prescribing to clinical databases. In addition, he urged increased R&D in the field and emphasized the importance of coordination and cooperation among the various stakeholders. AMR should not just be seen as a failure of the industry in general but also of science and biologists in particular. The last effective antibiotics were developed in the 60s; natural options for creating new antibiotics are running out.

### *Discussant*

***Gardner Brown, Ph.D. University of Washington, Seattle***

Regarding the Swanson and Goeschl paper, Dr. Brown described two key conclusions:

1. The introduction of new antibiotics to the treatment arsenal has important output and substitution effects (lower costs, more people, larger stock of effectiveness) and is analogous to new pesticides in agriculture.
2. The “lost horizons” detailed by the authors are reflected in both temporal and spatial missed opportunities. While temporal effectiveness is compromised by the patent system, which gives companies a limited window in which to earn monopoly profits, there is no mechanism to ensure spatial effectiveness. The spillover effects of resistance constitute the *spatial* lost horizon.

Dr. Bax proposed a ‘best policy function’ that would maximize the private benefits and minimize the social costs such as side effects and spread of resistance. He remarked that companies are again heavily investing in antibiotic research because the market has become more attractive with increasing resistance to existing antibiotics.

Dr. Uri Regev from the Ben Gurion University, Israel noted the ethical dilemma of a physician prescribing high doses of antibiotic to a patient and at the same time being aware of potential dangers of AMR resistance. The question is if a physician’s ethics only concerns the patient or if he also has an ethical responsibility towards the social environment that might be potentially affected by AMR resistance.

## **Session 3: Institutional responses to Antibiotic Resistance**

### ***“Resistance Issues and Product Labels”***

***Alex Rakowsky, MD, Division of Anti-Infective Drug Products, Food and Drug Administration***

Dr. Rakowsky focused on the use of FDA product labeling to promote judicious use of anti-infectives. The overall goal of FDA labeling of anti-infectives is to eliminate advertising or other promotion that imply greater effectiveness of one compound versus another based solely on *in vitro* microbiologic data. A claim of effectiveness for the treatment of infections due to resistant organism must meet specific criteria, including demonstrated activity *in vitro* and *in vivo* against susceptible and resistant strains.

The label includes critical information that can be used by health care professionals, managed care organizations, and consumers to guide decisions about AMR. Dr. Rakowsky noted that all product advertising, direct-to-consumer or otherwise, is driven exclusively by product labeling: if a claim is not included in the label, it cannot be promoted to any customer. Any data contained in the label, though, can be used to promote, and in this way label information can inform judicious antibiotic use. Other possible regulatory approaches to promote judicious use of anti-infectives include limited indications, limited distribution, and label inclusion of standard of care guidances. Overly restrictive labeling, however, could inhibit drug development since product label decisions are made early in the process, years before the clinical trials begin. Furthermore, restrictive labeling in one class of drugs may lead to overuse of other agents. Dr. Rakowsky closed by reminding the conference of the FDA's mandate to approve safe and effective agents, not to define the 'practice of medicine.'

Following the presentation Dr. Bax noted that the clinical trial process does not provide information on *optimal* use of antibiotic agents and therefore cannot be included in the label. Rather, optimal use questions are left to the market to discern. Dr. Tom O'Brien asked whether there could be skillful use of older agents to forestall resistance to the newer agents, such as the fluoroquinolones. Dr. Alex Rakowsky responded that once a drug goes off patent there is little financial incentive to study new areas of use.

***“Antibiotic Resistance: A Challenge for Global Health Jurisprudence”***

***David Fidler, M.Phil, J.D., Indiana University School of Law***

Dr. Fidler advocated that Global Health Jurisprudence define its role in partnership with Science and Economics in the international fight against AMR. Nationally and internationally, protecting the public's health depends on public health law. In connection with human and animal use of antibiotics AMR raises legal challenges that traverse global, national, and local legal levels and span all countries. Furthermore, these various levels of law are interdependent in connection to AMR. Dr. Fidler used four examples to illustrate the importance of law to AMR strategy:

- WHO's Global Strategy for the Containment of AMR;
- The EU Ban on the Use of Antibiotics in Animal Feed;
- U.S. FDA Efforts to Re-Evaluate the Regulation of the Use of Antibiotics in Food Animal Production, and;
- New York State Senate Committee Recommendations on Preventing and Controlling AMR.

The 'rule of law' holds that proper legal frameworks are critical for countries to protect human rights. Although a 'rule of law' movement in connection with public health is an exciting development, experiences of 'rule of law' activities in other contexts raise serious concerns about the structural, substantive, and cultural challenges to AMR-related policies. For example, a major substantive challenge is whether to regulate various aspects of the AMR problem or to continue to rely on the voluntary cooperation of health care providers, governments, and individuals. Because respect for the 'rule of law' is not uniform across the world, cultural divides are a serious challenge as well. Dr. Fidler suggested that a global legal strategy for AMR might include: a general duty to prevent, control, and reduce AMR; procedural duties on information sharing, notice, and consultation; on-going scientific and legal processes that develop substantive duties on AMR control, and; financial and technical assistance to developing countries.

Constructing a global legal strategy for AMR will be a significant challenge, as evidenced by health jurisprudence on HIV/AIDS. While global health jurisprudence on AMR is necessary, it is by no means sufficient to bring this problem under global control.

***“New Opportunities for Surveillance”***

***Dan Jernigan, MD, MPH, Office of Surveillance, National Center for Infectious Diseases  
Centers for Disease Control and Prevention***

New methods in laboratory-based reporting offer both opportunities for AMR surveillance and challenges. The primary purposes of AMR surveillance are to:

- Follow trends in the number of resistant cases,
- Evaluate clinical outcomes of resistant infections,
- Influence therapy choices,
- Determine drugs to include in routine susceptibility testing,
- Choose new drugs for clinical studies,
- Find associations between drug use and resistance,
- Identify preventive precautions, and;
- Prolong the useful life of antibiotics.

Traditional surveillance methods identify outbreaks and determine modes of transmission so that disease interventions can be carried out. Traditionally a ‘reporting labyrinth’ is involved using data from paper lab reports, clinician reports, vital statistics, discharge records, medical records, and surveys. Surveillance for AMR can exploit the traditional framework for surveillance, but alternative approaches should be considered as well. Dr. Jernigan proposed that AMR surveillance be used to capture important data at key points throughout the course of resistant infection, such as before the infection, on isolation of a pathogen, after the final laboratory report, and after the aggregation of data.

As the landscape of the laboratory reporting changes with increasing numbers of national microbiology laboratory mergers and the pooling of resources between academic and public health laboratories, new sources of resistance data and new information technologies may become available. Electronic laboratory-based reporting offers a fast and inexpensive means of aggregating data from these sources. Specifically, the National Electronic Disease Surveillance System (NEDSS) offers new possibilities. Improvements in public health infrastructure should include new information technologies that can facilitate surveillance for AMR.

***“Information Needed for Analysis and Management of Antibiotic Drug Resistance”***

***Thomas O’Brien, MD, Brigham and Women’s Hospital***

Dr. O’Brien introduced his presentation with a brief history of the process of antibacterial resistance and a reminder that the AMR problem is less about events in the human population than about events in the world’s *bacterial* population. A germ that is resistant to an antibiotic agent carries a gene that its susceptible ancestors lacked. That gene allows the destructive effect of the antibiotic agent to be blocked. Although sometimes the resistant gene spreads only in the strain in which it emerged, more often these genes are transferred on plasmids between strains and species. Use of an antibiotic agent amplifies the chance that a rare genetic event will result in the transmission of mutant genes. Each such event is historic, and in this way, hundreds of different resistance genes have emerged, spread, and recombined through the world’s interconnecting bacterial populations. Because we lack detailed observations and measurements about how these elements function together under various kinds of selective pressure, we do not have a basis for predicting the effect of antibiotic usage on changes in resistance.

Dr. O’Brien then introduced the WHONET project as an example of how we can acquire better information on AMR. Most information about AMR is found in the files of microbiology laboratories. Laboratories throughout the world isolate strains of bacteria from patient specimens each day, measure their susceptibility to antibiotic agents, report the results, and file archival

copies. Information on AMR at a specific medical center is contained in paper files, which are too laborious to analyze. The WHO Collaborating Center for Surveillance of AMR has worked to facilitate access to information now seclued in microbiology labs. Furthermore, WHONET developed a computer program to serve as a database for these files. A second program, BACLINK, was developed to facilitate the translation from each of the reporting systems. The intent of the project is to make available microbiology data so that microbiology, infection control, infectious disease and pharmacy divisions can use common data to monitor and manage AMR in a given center or community. Dr. O'Brien concluded with a call for medical-center based AMR management and the creation of a database for national, and ultimately supranational, 'resistometrics.'

### ***Discussant***

#### ***Dr. Thomas Hooton, MD, Department of Medicine, University of Washington***

Alluding to the conference focus on antibiotic agents, Dr. Hooton suggested that the biggest problem might not be overuse of antibiotics but rather effective infection control. He stated that AMR is not yet a full-fledged disaster: total drug resistance is a rare event, although VRE and vancomycin-resistant MRSA do sound alarms. Two pressing issues in clinical practice are penicillin resistance among *S. pneumonia* and TMP-SMX resistance among uropathogens. Concerns about the increasing resistance of these pathogens are leading physicians to prescribe the newer flouroquinolones. The AMR problem might be better served, however, by looking to older agents that do not carry AMR issues. The expense of this strategy, he acknowledged, is sub-optimal treatment.

Turning to the institutional responses presented by the panelists, Dr. Hooton recognized attendance by the FDA, CDC and the legal and hospital research communities, but called for active participation by the U.S. National Institutes of Health (NIH). Dr. Hooton then posed the following key questions and comments:

- Would direct to consumer advertising or public awareness campaigns be an effective alternative to FDA labeling strategies?
- Surveillance information is often dated, of limited availability, and raises quality, validity and generalizeability/applicability concerns.
- The legal community should recognize that the threat of malpractice in the U.S. does affect prescribing behavior.
- An independent research group, like the AIDS Clinical Trials Group in HIV research, should be considered as an important source of new, objective AMR data.
- Laboratory strategies should focus on the development of rapid, cheap, feasible, sensitive, and specific tests that discriminate between bacterial and non-bacterial infections.
- Change of usage patterns alone will not reduce AMR in the hospital; infection control must be supported.

Following Dr. Hooton's talk several participants, including Drs. O'Brien, Bell, and Williams, reflected on the complacency in the U.S. surrounding AMR. Only the U.S. and the developed countries have the luxury of waiting for the last effective antibiotic; developing nations do not have the option of a second or third choice. Furthermore the U.S. is losing the battle against first-line effectiveness. Already some patients are treated with less effective medications because of AMR. In the developing nations continued use of sub-optimal or resistant treatments only adds to the problem.

### **Session IV: Directions for Future Interdisciplinary Research**

***John McGowan Jr., MD, Emory University***

After noting that outside of the United States many developed countries have more comprehensive policies for addressing AMR, Dr. McGowan made the following recommendations for the field of AMR research:

- Antibiotic use is but one of many determinants of AMR. There is a lack of understanding on how these other determinants, such as vaccine use and host-environment modulators affect resistance levels.
- Epidemiologists and economists must be trained to work in the field of AMR.
- Discovery of new drugs is crucial to addressing the problem, but existing market-based incentives for research and development are inadequate. Alternative public and private institutions are necessary to advance knowledge in this area.
- Further work is needed to translate knowledge and research results to the specific problems of developing countries.

***David Bell, M.D., Centers for Disease Control and Prevention***

Dr. Bell discussed the role of economic incentives in the perpetuation of AMR. There is a conflict between drug discovery and proper drug use. On the one hand, controls on the use of antibiotics diminish incentives for research and development; on the other hand, health care providers continue to over-prescribe antibiotics, especially in outpatient settings where treatment may prevent more intense diagnosis and care. Furthermore, hospitals and physicians in developing countries depend upon pharmaceutical sales, of which antibiotics comprise a large proportion, for income. Likewise, agricultural sectors in developing countries depend upon antibiotics to maintain a plentiful and inexpensive food supply.

Dr. Bell noted that modeling AMR is difficult given that each “drug-bug” combination has its own dynamics. In response to a question from Dr. Sachs regarding the priorities of the CDC in the areas of agricultural use of antibiotics and cross-border issues, Dr. Bell stated that most resistance in humans comes from community and hospital transmission and that addressing cross-border transmission of resistance will be difficult given the diverging priorities of developing and developed countries.

***Thomas Philipson, Ph.D., University of Chicago***

Many speakers commented on the fact that use of antibiotics entails a negative externality in the form of reduced effectiveness for future patients. It follows, according to standard economic theory, that governments can restore socially optimal incentives by taxing antibiotic use. Dr. Philipson took issue with this interpretation of the AMR problem. Because research and development entails substantial knowledge spillovers (which by definition cannot be patented) there is *less* R&D of new drugs than is optimal. By providing a profit to pharmaceutical companies, consumption of antibiotics increases research and development incentives. The goal for policymakers, then, is to balance this positive externality of consumption against the negative externality of reduced effectiveness of existing antibiotics.

Some policies are unambiguously bad. Price controls, for example, lower both barriers to consumption of antibiotics and incentives to engage in research and development. Other policies will have ambiguous consequences for social welfare; taxes on antibiotic use help to preserve the effectiveness of existing antibiotics but diminish incentives to introduce new antibiotics. Given these competing concerns, it is not clear what direction policy should take.

***Rosamund Williams, M.D., World Health Organization***

Dr. Williams' addressed the problem of AMR in developing countries, which lack much of the basic infrastructure for tracking and curbing antibiotic overuse. Dissemination of information on proper use is an important first step. In developing countries, both physicians and patients must be targeted. To increase the effectiveness of education efforts, researchers need to understand patients' preferences for care. In many cultures patients expect to receive a pharmaceutical, often in intravenous form, as a routine matter of care. Understanding the economics behind physicians' prescription behavior and patients' use is also important. For example, it is unclear to what degree the cost of medications leads patients to take less than a full course of antibiotics.

**Open Discussion**

Professor Sachs opened the discussion by commenting on the inadequacy of current data for assessing the scope of AMR in developing countries. Many commenters echoed this concern and noted that even existing surveillance efforts are not carried out in such a manner as to produce data useful for epidemiological studies. Further complicating data collection efforts are the fact that it is difficult to generalize results from one type of 'drug-bug' combination to another. Modeling and assessing the problem of cross-resistance between diseases, countries, and sectors is also problematic. While there are now several informative models of AMR in the hospital setting, Dr. Sachs suggested that researchers select one disease and setting in which to model community acquired AMR. This information could potentially be used to extrapolate to other diseases. Professor Martin Weitzman added that even back of the envelope calculations based on spotty data could be very helpful.

Many speakers commented on the deficiency of price-related solutions to antibiotic overuse and asked that more attention be given in future research to non-price solutions. Dr. Darryl Farber raised the issue of providers' sensitivity to pharmaceutical prices. Dr. Hooton responded that demand responses to price changes vary by type of provider and insurer. If insurance mutes physicians' incentives to choose less-costly treatment options, as noted by Drs. Hooton and Laxminarayan, then taxes on antibiotic use and similar policies will be ineffective. Alternatives to financial incentives include better prevention techniques and vaccines. Dr. Williams commented that vaccines reduce antibiotic use by keeping people from getting sick in the first place and by helping physicians to rule out specific diseases in sick, but vaccinated patients. Improved diagnostic tests represent another type of technological improvement that would reduce misuse of antibiotics.

Much of the remaining discussion focused on whether or not existing patent laws and policies are adequate to ensure sufficient levels of research and development. Dr. Kathleen Young and others stated that they are not, and that the market undervalues drugs with a public health benefit. Likewise, according to Dr. Hooton, companies do not have incentives to develop "narrow-spectrum" antibiotics because the market is too small. Several policy options to address these problems were mentioned earlier in the day. Some commenters called for public and non-profit institutions to engage in research and development of new antibiotics. Another option, first noted in Dr. Bax's talk, is to provide pharmaceutical companies with a patent extension on a "blockbuster" drug if they develop a new antibiotic.

Dr. Philipson questioned whether governments could do a better job than markets in determining the social value of drugs and noted that even some "lifestyle" drugs such as Viagra produce large benefits to consumers. He pointed out that, in the intellectual property rights (IPR) system, negative consumption externalities such as AMR are to some extent recompensed positive externalities such as the incentive for companies to do more R&D. Professor Sachs responded that it would be better to finance extra rewards for companies that develop new antibiotics using a

broad-based tax rather than taxing users of one specific drug, but unlike Dr. Philipson, he did not rule out the value of antibiotic-specific incentives generally.

As for the problems in developing countries, Dr. Williams pointed out that 50 percent of the people in Sub-Saharan Africa do not have access to any kind of drug. The reason for this failure is probably the lack of purchasing power and the bad transport systems that impede adequate supply of drugs. Dr. Bell added the problem of developing country physicians' dependency upon drugs sales for income. This often results in misuse and overuse of antibiotics. Professor Sachs asked about the importance of agriculture and cross-border infection in developing countries. Such questions are difficult to answer, however, since AMR in the community setting and through the supply chain have not been investigated nearly as much as AMR in the hospital setting. Because of the enormous uncertainties of the medical market in developing countries, Professor Sachs encouraged biologists to develop new models that verify whether there are distortions among the perceptions and the empirical facts, perhaps starting with the example of tuberculosis.

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