POLICY RESPONSES TO THE GROWING THREAT OF ANTIBIOTIC RESISTANCE

Antibiotic Resistance and the 111th Congress

Each year in the United States, it is estimated that 90,000 people die from antibiotic-resistant infections, and the associated costs fall between $4 billion and $5 billion (Center for a Livable Future 2009; Laxminarayan 2010; Laxminarayan 2010b).

The health and economic burden of resistance has not escaped the attention of federal legislators, who have proposed policies to slow the emergence and spread of resistance and resistant infections in communities, health care facilities, and food-producing animals. Bills introduced during the 2009–2010 session of Congress focused on three important strategies for curbing resistance: (1) encouraging judicious antibiotic use; (2) reducing hospital infections using public reporting programs; and (3) stimulating the development of new antibiotics (Table 1). In comparison with legislation introduced in previous sessions, the bills of the 111th Congress increasingly make use of incentives, a valuable tool in motivating behavior change.

This policy brief compares bills introduced during the 111th Congress and serves as a primer for the work of the 112th Congress, where similar approaches to combating antibiotic resistance will likely be proposed.

Judicious Use

Two bills—the Preservation of Antibiotics for Medical Treatment Act (PAMTA) and the Strategies to Address Antimicrobial Resistance (STAAR) Act—were reintroduced during the 111th Congress. Both address inappropriate antibiotic use, a major driver of antibiotic resistance, and pay special attention to how antibiotic use in the livestock sector affects the development of antibiotic-resistant infections in humans (Center for a Livable Future 2009). They also call for public reporting of antibiotic sales, distribution, and use data.

PAMTA (H.R. 1549)

PAMTA focuses exclusively on antimicrobial use in food-producing animals and would phase out nontherapeutic livestock uses of seven classes (and all their derivatives) of antibiotics used in human medicine or that have human use equivalents.

In addition to banning the nontherapeutic use of medically important antibiotics in food-producing animals, the bill also requires that FDA review and rescind previous approvals if the drugs used could harm human health through the development of resistance. Furthermore, it requires that FDA not approve any new animal antibiotic drugs unless the applicant can demonstrate “reasonable certainty of no harm to human health.” These provisions aim to curtail the misuse of antibiotics in the sector and thus avert the development and transmission of resistance from food animals to people.

This bill could be extended to cover the use of these same classes of drugs in other agricultural activities, for instance in growing crops or orchard fruits. Including these other activities would ensure better coverage of the possible micro biomes within which the spread of antibiotic resistance can take place. The bill should also support research efforts to address the research gaps concerning the actual effect, if any, of antibiotics on growth in animals and to quantify the human health consequences of antibiotic use in livestock and agriculture.

PAMTA proposes an all-or-nothing approach, banning nontherapeutic, medically important antibiotics in livestock, but could consider reducing overuse by implementing a tax on antibiotics instead. The bill also does not take into account its effects on antibiotics sales. Decreased sales may discourage development of new antibiotics by pharmaceutical companies, which

stand to lose revenue with the bill's passage. It should, therefore, include incentives for companies to continue antibiotic research and development.

STAAR (H.R. 2400)
The STAAR bill seeks to address critical gaps in knowledge of how antibiotics are prescribed and used. It calls for funding and strengthening existing federal data collection, resistance surveillance systems, and research activities, and would establish several antimicrobial resistance offices, a public health antimicrobial advisory board, and several national antimicrobial surveillance and research network sites.

A coordinated national network of surveillance sites is necessary to enhance the collection of data to better capture national resistance trends, patterns, and possible regional variations. Coordination allows for comparable data points across the nation through the establishment of a uniform data set. Network researchers would also conduct basic and clinical research on both livestock and human health, including the human health consequences of antibiotic use in animals.

The STAAR bill, although comprehensive in its requirement for surveillance of both animal and human use, does not address the issue of translating surveillance data into more optimal antibiotic use practices. The new offices would work with CDC, NIH, and FDA, but they do not have authority to regulate antibiotics.

Public Reporting of Hospital-Acquired Infections

A report of the U.S. Department of Health and Human Services (2010) found that for three of the five major types of serious hospital-related infections, the rate of illness increased in 2009. Hospitals have poor infection control programs and lack financial incentives to improve them, in part because they can recover the cost of hospital-acquired infections (HAIs) from some third-party payers.

In response to the growing burden of HAIs, 27 states have passed legislation requiring public reporting of infection rates. The motivation behind public reporting laws is that transparency helps patients make informed decisions about where to receive treatment, thus encouraging hospitals to improve their infection control strategies. However, a nationwide attempt to eliminate HAIs requires a federal mandate for hospitals to report their infection rates. In this way, regardless of the state, patients will have better information, increasing incentives for hospitals to establish infection control programs. Additionally, federal regulation will promote standardization of methods and data and allow for comparison of data across hospitals nationwide.

Three bills—the Healthy Hospitals Act of 2009, the MRSA Infection Prevention and Protection Act, and the Patient Protection and Affordable Care Act (signed into law)—propose mandatory public reporting of hospital infections at the federal level.

MRSA Infection Prevention and Protection Act (H.R. 2937)
The MRSA Infection Prevention and Protection Act would impose mandatory MRSA screening of patients and reporting of MRSA rates. It also proposes a system to identify, inform, and report facilities that transfer MRSA-infected patients. These provisions will allow for the rapid identification and isolation of patients who are MRSA carriers through screening, thus preventing the transmission and spread of these organisms within the hospital and beyond.

The bill offers federal loans to eligible hospitals to support rapid program implementation. However, it is unclear why the federal government should extend financial assistance to hospitals in the form of loans and not subsidies. Surveillance provides a public good—information—and in the absence of subsidies, the quality of information collected may be poor. Because this information should be the basis for requiring quality improvements, the government should ensure that hospitals have incentives to conduct effective surveillance.

The act would also federalize specific standards of care. This is problematic and inefficient, since some states that need to apply state-specific adjustments will have to go through Congress to do so. Additionally, when new scientific evidence warrants a new best practice protocol, the change would have to be approved by Congress before it could be adopted in health care centers.

Healthy Hospitals Act of 2009 (H.R. 3104)
Unlike H.R. 2937, the Healthy Hospitals Act does not focus exclusively on MRSA but covers all HAIs in hospitals and ambulatory surgical centers. Reporting on infections beyond MRSA is generally a more accurate representation of hospital quality and safety regarding HAIs. This legislation proposes to penalize hospitals and ambulatory surgical centers that fail to fully report required data. Although financial penalties can be effective, it is not certain whether the level of penalties proposed (a maximum of $5000 for each violation) are large enough to make a difference. The bill also excludes extended-care facilities, such as nursing homes and rehabilitation homes, which are important reservoirs of HAIs. The Healthy Hospitals Act may not be reintroduced because of significant overlap in its provisions with the Patient Protection and Affordable Care Act that was signed into law last year.

Patient Protection and Affordable Care Act (Public Health Law 111-148)
The major health reform legislation of 2010, the Patient Protection and Affordable Care Act, is the only one of these bills signed into law last year, and it offers a more comprehensive carrot-and-stick approach to deal with infection control. In addition to mandating public reporting of infections, the new law calls for monetary rewards and penalties for high- and low-performing hospitals. The government will award higher Medicare payments to hospitals that demonstrate a reduction of HAIs over time but will reduce payments to those that have the highest rates of acquired infections. However, this provision is applicable only to Medicare payments and thus does not cover other large segments of the health system. Whether these payments are significant enough to incentivize hospitals to reduce their infection rates is not known. Also, care will have to be taken to ensure that financial incentives tied to measures of infection rates do not end up penalizing hospitals that serve disadvantaged populations. This is an important detail, since hospitals with fewer resources could potentially face greater barriers to improving HAI rates over time.

The reporting requirements, although an important strategy in reducing HAIs, could cause hospitals to avoid admitting high-risk patients in order to maintain low infection rates. They may also spend less on disease surveillance if they expect to report a large number of infections. These issues need to be addressed in the structuring of the reporting programs.

The new law also authorizes the Center for Quality Improvement and Patient Safety, which will identify the most effective practices to prevent HAIs and improve quality of patient care. This information will be disseminated to all hospitals. Thus, the law addresses not only incentives for infection control but also other measures to improve health care quality.

Development of New Drugs

Despite the decreasing effectiveness of antibiotics, investment in the research and development of novel antibiotics has fallen significantly (Morel and Mossialos 2010). Only two new antibiotics are currently undergoing clinical trials—both in the early stages, when failure rates are high (Morel and Mossialos 2010; Interlandi 2010).

Two measures—the Generating Antibiotic Incentives Now Act and a resolution, Expressing the Need for Biotechnology Firms—propose strategies to encourage the development of new antibiotics. The bill focuses on creating incentives for existing pharmaceutical companies to invest in research and development of new antibiotics; the resolution[1] encourages the creation of small biotechnology firms as an alternative solution.

Generating Antibiotic Incentives Now Act (H.R. 6331)
To encourage drug companies to invest in antibiotic development, the Generating Antibiotic Incentives Now (GAIN) bill proposes five-year exclusivity extensions for new “qualified infectious disease products,” guaranteed government purchases, and priority review for the licensing and approval of antibiotics. The GAIN bill is similar to the 1983 **Orphan Drug Act (Public. Law 97-414)** in terms of incentives as it also offers market exclusivity to pharmaceutical companies that approve orphan drugs—drugs for rare conditions that affect fewer than 200,000 patients in the United States.

It is important, however, that the ‘qualified disease product’ in the GAIN bill be limited to novel innovations, i.e. new classes of antimicrobials for currently resistant infections. This element is essential because similar drugs favor similar mechanisms of resistance and so

[1] Unlike a bill, a House resolution (H. Res.) does not go to the Senate and cannot be signed by the president into law. Its purpose is to express thegeneral sentiment of the House of Representatives about a particular issue.

cross-resistance is very likely to occur, reducing the effectiveness of the overall class. This situation, in which firms make products with similar modes of action, is a common property issue: firms exploiting a common resource (here, the effectiveness of a class of antibiotics) have no incentive to conserve it. Limiting the definition to truly novel innovations will incentivize drug companies to invest in new antimicrobial classes that do not share cross-resistance with the existing ones.

It is positive that the product itself gets priority review in this bill as opposed to the transferable priority review voucher mechanism under the **FDA Amendments Act of 2007**. With the FDA provision, companies that obtain approval for one novel drug are rewarded with a voucher that can be used to obtain an expedited review of another drug. Priority review of the product itself is preferable to the voucher system because of the unintended consequence of the voucher. Companies are incentivized to develop "me-too" drugs, drugs that would never have been eligible for expedited review in the absence of the voucher. In the case of antibiotics, the continued development of drugs that share similar therapeutic qualities as those already on the market (and are already exhibiting resistance) will reduce the effectiveness of the class. Priority review of solely the product being developed protects against this drawback.

The bill would also be quite costly to the government. A paper issued by the Office of Health Economics estimates that the cost of incentives needed to make the net present value for antibiotic development more competitive relative to other disease areas ranges from $980 million to $2.5 billion (Sharma and Towse 2010).

H. Res. 1179

This House Resolution expresses support for the creation of small biotechnology firms that provide new and promising therapeutics for drug-resistant pathogens and also offer new approaches to the development of antibiotics. The solution the resolution encourages could indirectly tackle the common property issue if the new firms focused solely on innovations in antibiotic development. However, the resolution says that the creation, development, and preservation of these firms would require public funding. Public funding for antibiotic development would likely be a costly venture for the government. In August, the Biomedical Advanced Research and Development Authority gave an initial $27 million to Achaogen for the development of just one antibiotic (Pollack 2010). Additionally, issues surrounding patent ownership are bound to arise between government and private firms when the government is funding the basic research.

Looking Forward

The diversity of issues raised by the bills introduced in the 111th Congress points to the need for comprehensive, integrated strategies that reduce rates of transmission of resistant infections in hospitals and communities, delay resistance through the prudent use of existing antibiotics, and ensure a steady supply of effective drugs through research and development. Focusing on each solution individually ignores the interrelatedness of different approaches to manage antibiotic effectiveness as a societal resource.

For example, absent from both H.R. 6331 and the House resolution are incentives for drug companies to conserve the effectiveness of the antibiotics that they develop. Without regulations in place to ensure that the companies that develop new drugs also guarantee their prudent use, these new drugs will be subject to the cycles of resistance that have compromised existing drugs. Additionally, bills encouraging more innovation in antimicrobials could focus not only on the development of new antibiotics but also on other innovative measures, such as the development of new vaccines and better diagnostic tools.

During the 111th Congress, most of the measures noted above did not move past the deliberation and revision stage. It is likely that in the 112th Congress we will see the reintroduction of many of these measures and the introduction of new bills with similar approaches. Developing an integrated, effective strategy for combating antibiotic resistance—a public health issue that spans industries and stakeholders—will require the careful attention of current Congress members.

Table 1. Comparison of Some Antimicrobial-Resistance Related Bills Introduced in 111th Congress

Category	*Measure*	*Target sector and relevant federal agencies*	*Aim, purpose*	*Antibiotic resistance-related provisions*	*Pros*	*Cons*
Judicious prescribing	Preservation of Antibiotics for Medical Treatment Act of 2009 (H.R. 1549) (Read Bill)	Food-producing animals	To preserve effectiveness of antibiotics important for human health	Withdrawal of nontherapeutic use of 7 classes of critical antimicrobial drugs in food-producing animals within 2 years of enactment	Preserves effectiveness of antibiotics used in humans	Provides no drug development incentives
		USDA, HHS, FDA		Payments to livestock producers to help them transition away from use of these antibiotics		Focuses exclusively on animals
				Annual public reporting (to FDA) of antibiotic distribution and sales		
	Strategies to Address Antimicrobial Resistance Act (H.R. 2400) (Read Bill)	Food-producing animals, human public health sector	To enhance efforts to address antimicrobial resistance by reducing inappropriate antimicrobial use in humans and animals	Establishment of antimicrobial resistance office, public health antimicrobial advisory board, and antimicrobial surveillance and research network sites	Improves government resistance surveillance and antibiotic use data collection systems	Provides no drug development incentives for animal and human sectors
		CDC, FDA, NIH, EPA, USAID, DHS, USDA, Education, Defense, Veterans Affairs, Centers for Medicare and Medicaid Services		Annual publishing of all report summaries received by different agencies	Researching effect of resistance on human health resulting from approval of antimicrobial use in animals	Gives agencies no new regulatory authority

Development of new antibiotics	Generating Antibiotic Incentives Now Act of 2010 (H.R. 6331) (Read Bill)	Existing drug companies	To provide incentives to drug companies to continue development of new antibiotics	5-year extension of patents; priority review and fast track for approval and licensure of new antibiotics	Provides incentives for drug companies to develop new antibiotics	May cost more than $1 billion per drug
		FDA, HHS		Annual progress report to Congress of review of FDA guidelines	Reduces cost of development of new antibiotics	Creates no incentives for drug companies to explore new antibiotic classes
				Revision of guidelines to reflect developments in scientific and medical information and technology	Increases return from development of new antibiotics	Creates no incentives for companies to take part in antibiotic conservation efforts
	Expressing need for biotechnology firms (House Res. 1179) (Read Resolution)	New Biotechnology firms	To encourage creation of small biotechnology firms that will invest in development of new antibiotics	Recognition of need for new and promising therapeutics for drug-resistant pathogens and approaches to antibiotics based on defensin mimetics	Could lead to exploration of new mechanisms of drug development	Requires public funding, may be costly
		All federal agencies of jurisdiction		Encourages development of federal biotechnology coordinating council	Would lower firms' cost of new antibiotics with government funding	May lead to patent ownership issues
Hospital infection control	Patient Protection and Affordable Care Act (Public Law No. 111-148) (Read Law)	Medicare	To reduce hospital-acquired infections	Mandatory public reporting of hospital-specific HAI rates	Creates incentives to reduce HAI rates	Addresses only Medicare patients, leaves out large segments of health care system
		All health-related state and federal agencies		Establishment of center for quality improvement and patient safety	Focuses on measures to determine patient quality care other than infection rates	May make hospitals more selective against high-risk HAI patients

				Dissemination of information on best practices to hospitals	Increases transparency	Creates perverse incentive to reduce HAI surveillance
				Financial rewards and penalties to high- and low-ranking hospitals, respectively		
	Healthy Hospitals Act of 2009 (H.R. 3104) (Read Bill)	Hospitals, ambulatory surgical centers	To reduce occurrence of HAIs	Mandatory reporting of HAI data for hospital and surgical ambulatory centers	Increases transparency	May make hospitals more selective against high-risk HAI patients
		HHS, CDC		Civil penalties up to $5,000 for failure to report all required data	Creates incentives to reduce HAI rates	Focuses only on infections for determining quality of health care facility
				Submission of annual report to Congress		Creates perverse incentive to reduce HAI surveillance
	MRSA Infection Prevention and Protection Act (H.R. 2937/S 1305) (Read Bill)	Hospitals	To prevent HAIs	Mandatory MRSA screening of patients admitted to ICU and other high-risk units	Creates incentives to reduce MRSA rates in hospitals	Focuses only on MRSA infections
		CDC, Secretary of HHS		Public reporting of MRSA hospital-specific infection rates	Eliminates hospitals' free-riding incentive	May make hospitals more selective against high-risk HAI patients, creates perverse incentive to reduce HAI surveillance
				Development of system for identifying, informing and reporting facilities that transfer already infected patients	Increases transparency	Focuses only on infections for determining quality of health care facility

References

1. Center for a Livable Future. 2009. "Congressional Briefing: Antibiotic Resistance: A Multi-Billion Dollar Health Care Crisis." December 2009. http://www.livablefutureblog.com/CLF%20Briefing%20Book.pdf (accessed December 19, 2010).

2. Interlandi, J. 2010. "Are We Running Out of Antibiotics?" *Newsweek*. December 7. http://www.newsweek.com/2010/12/07/are-we-running-out-of-antibiotics.html (accessed December 22, 2010).

3. Laxminarayan, R. 2010a. "Avoiding the Unnecessary Costs of Hospital-Acquired Infections." Policy Commentary. Washington, DC: Resources for the Future. March. http://www.rff.org/Publications/WPC/Pages/Avoiding-the-Unnecessary-Costs-of-Hospital-Acquired-Infections.aspx (accessed December 29, 2010)

4. ———. 2010b. "Healthcare Associated Infections: States and Public Reporting." PowerPoint presentation. Center for Disease Dynamics, Economics & Policy. October. http://www.cddep.org/tools/hais_states_and_public_reporting (accessed December 19, 2010).

5. Laxminarayan, R., and A. Malani. 2007. "Extending the Cure: Policy Responses to the Growing Threat of Antibiotic Resistance." Discussion Paper. Washington, DC: Resources for the Future.

6. Morel, C., and E. Mossialos. 2010. "Stoking the Antibiotic Pipeline." *British Medical Journal* 340: c2115.

10. Pollack, A. 2010. "Antibiotics Research Subsidies Weighed by U.S." *The New York Times*. November 5. http://www.nytimes.com/2010/11/06/health/policy/06germ.html (accessed January 24, 2011).

11. Sharma, P., and A., Towse. 2010. New Drugs to tackle antimicrobial resistance: Analysis of EU policy options. OHE Occasional Paper 10/01. London: Office of Health Economics. http://www.ohe.org/publications/recent-publications/list-by-date-20/detail/date///new-drugs-to-tackle-antimicrobial-resistance-analysis-of-eu-policy-options-1.html (accessed September 12, 2011).

12. U.S. Department of Health and Human Services. 2010. "2009 National Healthcare Quality Report." Agency for Healthcare Research and Quality. March. http://www.ahrq.gov/qual/nhqr09/nhqr09.pdf (accessed December 20, 2010.

CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy WASHINGTON DC • NEW DELHI

YOLISA NALULE
Center for Disease Dynamics, Economics & Policy (CDDEP)