CHAPTER 5

The role of the **federal government**

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Earlier chapters have described the externalities generated by antibiotic overuse and insufficient infection control and have made the case for why individual actors (including patients, physicians, and hospital administrators) may lack sufficient incentives to manage for resistance. In the absence of our ability to assign strict liability for antibiotic overuse or lack of infection control to those different actors, the market failure evident in the negative externalities provides a strong rationale for government involvement to ensure that antibiotics are produced and used in a sustainable manner.

There is a role for both federal and state agencies to act on the antibiotic resistance problem; this chapter focuses on the former. The Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH) are already engaged in a response to the resistance problem. CDC has been promoting campaigns to lower antibiotic use in hospitals and outpatient settings; FDA has acted to introduce labeling on antibiotics to warn consumers of the emergence of drug resistance, and has disallowed the use of antibiotics in animals in an instance where there was a likely threat to human health; and NIH has diverted modest funding to support discovery of new antibiotics. However, no single government agency currently has the ability or resources to respond adequately to the threat of antibiotic resistance.

Since 2001, recognizing the need for a coordinated response to the problem, a number of federal agencies, under the leadership of CDC, NIH, and FDA, have operated under the auspices of the Interagency Task Force on Antimicrobial Resistance (ITFAR).[1] The action plan drafted by the task

1 The task force also includes representatives from the Agency for Health care Research and Quality, the Centers for Medicare and Medicaid Services (formerly the Health Care Financing Administration), the Department of Agriculture, the Department of Defense, the Department of Veterans Affairs, the Environmental Protection Agency, and the Health Resources and Services Administration.

force describes specific, coordinated actions to be undertaken by federal agencies covering a range of issues—from better lab standards for resistant pathogens to educational interventions for helping physicians with appropriate antibiotic prescribing. Several action items on the plan also relate to economic incentives, specifically removing barriers to the use of diagnostics in clinical care settings and improving incentives for new drug development. In this chapter we examine possible roles for the federal government in addressing some of the externalities implicit in the antibiotic resistance problem.

What government can do

An important reason for government involvement in antibiotic resistance is that antibiotic effectiveness is a common property resource. In this regard, it shares features with other resources, such as forests or fish, where excluding users may be difficult and the potential for overexploitation is serious; hence federal agencies, such as the Forest Service or the National Oceanic and Atmospheric Administration have a clear management role. There is a long documented history of successes and failures in the management of common property resources that efforts to manage antibiotic effectiveness can draw from. A fundamental challenge of managing resources is to find the appropriate mix of policies that alter incentives for individual decisionmakers to consider the effect of their actions on everyone else, and policies that call for oversight and action by government agencies.[2]

An important distinction in the case of antibiotics is that the drugs themselves are developed and sold by private economic agents, but this does not preclude Congress from acting to help sustain the effectiveness of antibiotics. Federal law gives CDC, NIH, and FDA clearly defined and separate roles in addressing public health problems, and these agencies can work on the following three objectives as appropriate to their missions: 1) improving the quality of antibiotic use, 2) improving hospital infection control to prevent emergence and transmission of resistant pathogens, and 3) improving the supply of new antibiotics.

> A stronger mandate and funding to improve surveillance for drug resistance is an important first step.

:: IMPROVING ANTIBIOTIC USE

The two federal agencies that are best positioned to help improve the quality of antibiotic use are CDC and FDA. CDC is charged, broadly speaking, with surveillance and response to epidemics and disease outbreaks. This gives CDC a mandate to work, largely in a technical advisory capacity, to prevent the emergence of drug resistance and to be actively involved in containing outbreaks of resistant pathogens. Surveillance for antibiotic resistance in both hospitals and communities is already an important function. However, CDC cannot require hospitals to report resistance levels, and under its current arrangements it cannot publicly release any disaggregated data on hospital infection or resistance levels. A stronger mandate and funding to improve surveillance for drug resistance is an important first step.

Another useful role for CDC is educating physicians about the dangers of drug resistance and the importance of appropriate prescribing, even though educational measures go only so far in changing behavior. CDC can also pay for research to improve the use of antibiotics in hospital

2 Both types of policies are challenging to implement in the context of medical practice, for reasons we discuss later.

and outpatient settings; in fact, it has done so in the past (to evaluate the use of antibiotic cycling programs to delay the emergence of resistance), although the quantity of such funding has been quite small.

CDC's strongest role is in influencing clinical practice based on a broader, multidisciplinary view of resistance, rather than just through a biomedical lens. For example, CDC could take the lead in integrating ecological understanding into antibiotic use and promote fundamental change in our thinking, including a rethinking of clinical guidelines for antibiotics. Current guidelines encourage the use of the least expensive or most cost-effective antibiotics, and thus a small number of antibiotics are prescribed extensively. Ecological theory, however, suggests that this practice may promote the development of resistance much more rapidly than if a diverse set of antibiotics were used. Moreover, treatment guidelines that call for "conserving" some antibiotics for infections that are not treatable by less expensive drugs inadvertently create disincentives for research and development efforts on new antibiotics (see Chapter 7).

FDA can regulate antibiotic use in the interests of patient safety. It has done so in the context of drug resistance in two instances. In 2000, FDA intervened to require two pharmaceutical companies to stop selling fluoroquinolones for growth promotion in poultry because of concerns that this was causing drug-resistant *Campylobacter* infections in humans (Box 5.1). In 2003, FDA issued new labeling regulations designed to help slow the development of drug-resistant bacterial strains by reducing the inappropriate prescription of antibiotics to children and adults for such common ailments as ear infections and chronic coughs.[3]

3 FDA can also require testing after approval of fast-track drugs but has no enforcement power, so this approach is infrequently taken. In addition, it is unclear what mandate FDA has to even regulate drugs once they have been approved. There is certainly no organizational motivation or structure in place to do this.

:: IMPROVING INFECTION CONTROL IN HOSPITALS

CDC has a public health mandate to address hospital-acquired infections (HAIs) whether or not they are drug resistant. CDC may be better positioned to respond to public health emergencies caused by an outbreak of resistant pathogens, however, than to encourage hospitals to take long-term measures to contain drug resistance. The largely advisory and educational role that CDC can play in ensuring hospital infection control and judicious antibiotic use (except perhaps in a time of crisis) has constrained a strong federal response to the problem. However, CDC may be able to change incentives for private providers and hospitals to invest more strongly in infection control.

For instance, CDC can promote the use of regional cooperatives between hospitals to ensure that efforts to control HAIs are coordinated at a regional scale rather than at the scale of a single hospital. As discussed in Chapter 4, an individual hospital may have little incentive to invest in HAIs if it admits patients colonized at other facilities that have poor infection control measures. The "commons" problem associated with HAIs can be addressed by state-level health authorities but with a coordinating function played by CDC.

BOX 5.1

REGULATING BAYTRIL: INCENTIVES FOR BAYER

In 2000, FDA announced that the proportion of *Campylobacter* infections resistant to fluoroquinolones—a powerful class of antibiotics for use in human treatment and for growth promotion—had increased significantly since one type of the drug, enrofloxacin, had been approved for use in poultry in the United States. Over growing concerns about the impact of this use on human health, FDA withdrew permission for Bayer to sell Baytril, their enrofloxacin product, for growth promotion. It was only after a lengthy court battle that ended in 2005, however, that Bayer finally agreed to comply with FDA's ruling. One would have expected Bayer to be concerned about the impact of resistance on demand for Cipro (which belongs to the same class of antibiotics as Baytril), its highly successful fluoroquinolone sold for human use.

Although the quantity of antibiotics sold for growth promotion is large, the economic value of this market to antibiotics producers is much smaller than that for human antibiotics, which sell at a higher price. For instance, in 2000, Bayer's sales of Cipro (the brand name of ciprofloxacin) amounted to roughly 1.8 billion euros, compared with only 170 million euros for sales of Baytril. Why would firms acting in their own self-interest jeopardize their profitable human drugs market to retain a much smaller market for growth-promoting agricultural drugs? After all, if firms fully internalized the consequences of future resistance, then there would be no need for regulatory intervention to protect the future effectiveness of these valuable drugs.

One answer is that there may be market failure. Often, many firms make different antibiotics that are derivatives of the same basic chemical entity. For instance, there are currently at least four firms that make fluoroquinolones. Because the resource embodied in the effectiveness of a class of antibiotics is available to several pharmaceutical firms, no single firm has incentive to take into full consideration the effect of its sales of antibiotics on future antibiotic effectiveness—even though resistance may be an inevitable consequence of antibiotic use.

Another major reason is patent expiration. Pharmaceutical companies have an incentive to sell as much of a drug as possible before their patent expires and generics enter the market. They may be much less concerned about engendering resistance to their products. In the case of Bayer, Cipro and Baytril were scheduled to go off-patent in 2004 and 2006, respectively. Thus, Bayer correctly predicted that their sales of Cipro would dramatically fall after going off-patent (sales dropped to 525 million euros in 2005). Since Baytril use had little effect on resistance, sales, and profits of Cipro in the short term, Bayer had no incentive to stop selling the drug. Instead, Bayer had an incentive to fight the FDA ruling since Baytril recorded more than a billion euros in sales between 2000 and 2005.

Antibiotic effectiveness is a common property resource, and the classic externality problem arises when, from a societal perspective, too many doses of antibiotics are sold. From an economic perspective, the price of antibiotics sold for growth promotion may not adequately reflect the true social cost of resistance associated with such use, and it is likely that sales of antibiotics for growth promotion in food animals would decline if farmers and pharmaceutical companies faced the full resistance-related costs.

CDC can conduct surveillance and set guidelines but may be more constrained from the standpoint of enforcement. The Centers for Medicare and Medicaid Services in the Department of Health and Human Services can help provide incentives by tying Medicare and Medicaid reimbursements to physician antibiotic prescribing and hospital infection control practices; this is discussed in greater detail in Chapter 6.

:: IMPROVING THE SUPPLY OF NEW ANTIBIOTICS

Development of new antibiotics appears to be on the decline. According to a recent review, FDA approval of new antibacterial agents decreased by 56 percent between the periods 1983–1987 and 1998–2002 (Spellberg, Powers et al. 2004). Only 6 of 506 drugs disclosed in the developmental programs of the largest pharmaceutical and biotechnology companies are antibacterial agents, and all of these new drugs belong to existing classes of antibiotics.

NIH and FDA are positioned to act to improve the supply of new antibiotics (Chapter 7). The National Institute of Allergy and Infectious Diseases, one of the largest institutes of NIH, has funded work on the basic biology of resistant organisms as well as applied research on new diagnostic techniques, therapies, and preventive measures. NIH support for basic research is an important subsidy to drug development and should be continued. NIH can lower the cost of product development by paying for basic scientific research to identify new target organisms and drugs that can work on these targets.[4]

FDA's role in new drug development is more complex, since it must ensure the safety and efficacy of new antibiotics without discouraging new drugs. FDA currently requires that manufacturers of new antibiotic demonstrate that their medications are noninferior to currently available antimicrobials. Some have argued that this places a heavy burden on new antibiotic development and has discouraged

> Faster approvals may be less desirable than direct financial incentives from a societal perspective.

pharmaceutical manufacturers from investing in this therapeutic area (Projan and Shlaes 2004). However, others contend that many antibiotics approved for use have not been evaluated adequately. Therefore, showing noninferiority by some specific margin against an intervention that may not be better than a placebo is no indicator of effectiveness at best, and at worst could be worse than a placebo (Powers, Cooper et al. 2005). This report does not address the question of appropriate standards for new antibiotics directly except to point out that the issue of weighing the benefits of having a new drug against safety concerns is not unique to antibiotics.[5]

However, FDA does have a role in ensuring patient safety by making new antibiotics available for pathogens that are not treatable using existing drugs. In this role, an objective of FDA's Critical Path Initiative is to ensure faster approval and reverse the declining number of drug approvals each year.[6] Although it certainly makes sense for FDA to do what it can within its protocols to speed up the rate at which antibiotics move through the approval process and lower development costs for pharmaceutical manufacturers, the faster rate of

4 In truth, there is no lack of targets; the problem lies in the ability to create a drug that can attack those targets without being toxic to the patient.

5 Safety concerns have arisen after a new antibiotic has been approved, as was the case with Ketek, a macrolide introduced by Sanofi-Aventis in 2004. Nevertheless, it is important to ensure that regulations intended to prevent unsafe drugs do not delay new antibiotics in the pipeline. Delays can have significant costs in discouraging manufacturers from investing in this area.

6 http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf.

approval could come at the cost of patient safety. Industry incentives to develop new antibiotics are enhanced by faster approval (by reducing the safety and efficacy requirements) or more attractive financial incentives or both. Faster approvals may be less desirable than direct financial incentives from a societal perspective.[7]

Providing economic incentives to encourage firms' research and development on antibiotics is outside the mandate of any federal agency and has to be separately authorized by Congress. The Bioshield II bill[8] cosponsored by Senators Joseph Lieberman and Orrin Hatch, which received strong support from the medical profession, the American Association of Tropical Medicine and Hygiene, and the Infectious Diseases Society of America, called for statutory incentives to promote the development of new antibiotics, including tax credits for research and development, wildcard patents that could be used to extend patent life on other "blockbuster" drugs made by the company, lowered cost of clinical trials through FDA flexibility on the evidence necessary to demonstrate safety and efficacy, and liability protections to lower pharmaceutical industry risk, among other measures. However, these incentives did not require any industry commitment to ensure that the new antibiotics would not be overused or marketed for uses that might hasten the emergence of resistance. Nor did they require that the new antibiotics come from new classes rather than from the current 16 classes of compounds. The commons problem that exists when several companies are making related antibiotics having the same genetic basis for resistance was not addressed by this proposed legislation.

An alternative is to tie benefits to pharmaceutical firms to the level of effectiveness of their products. Such measures would give the industry incentive to care more about drug resistance. Providing incentives for new drugs without requiring investments in ensuring appropriate antibiotic use is likely to result in a repeat of the current situation in a decade or two, and moreover, it is unlikely that new drug development can ever keep pace with the rate at which bacteria develop resistance to new drugs. However, the greater the restrictions on new antibiotics, the larger the incentives needed to keep the pharmaceutical industry involved in the pursuit of new antibiotics.

Recent legislation by Congress created the Biomedical Advanced Research and Development Agency (BARDA) to act as the "single point of authority" to promote advanced research and development of drugs and vaccines in response to bioterrorism and natural disease outbreaks. The legislation has the potential to encourage new research into antibiotics by shielding drug manufacturers from liability lawsuits if a

7 Speeding up approval by FDA without investing more resources in the approval process could compromise patient safety. The hurdle is the massive amount of information that agency staff must absorb about a drug before a reasonably informed determination can be made about its usefulness and safety.

8 http://www.govtrack.us/congress/bill.xpd?bill=s109-975.

> EPA regulations regarding *Bt* are the first from any U.S. agency that treat pest susceptibility as a public good.

drug used to counteract bioterrorism or epidemics caused death or injury. The agency could also potentially fund new drug development directly—with billions of dollars, at a scale similar to the Defense Advanced Research Projects Agency—if the problem of resistance were a national security issue. However, as with Bioshield II (upon which the new bill drew heavily), fundamental problems associated with the common property nature of antibiotic effectiveness and the need to develop new classes of antibiotics are not addressed.[9]

A possible model: EPA and pest resistance to *Bt*

The Environmental Protection Agency (EPA) offers the only example of a federal agency that has regulated for effectiveness of a biological control agent by acting preemptively to prevent the emergence of pest resistance to transgenic crops. The Federal Insecticide, Fungicide, and Rodenticide Act gives EPA authority to amend or revoke existing registrations of pesticides in the event of "unreasonable adverse effects." The law also permits EPA to impose new measures as new information becomes available. EPA has used this law in recent years to regulate for pest resistance to *Bacillus thuringiensis,* or *Bt*. A gene from this bacterium codes for the production of a protein highly toxic to many insect pests and has been inserted in cotton, tobacco, corn, and soybean varieties. Unlike chemical pesticides, which may be blown away or washed off or lose effectiveness after being sprayed on crops, the pesticide is always present in these *Bt* varieties.

Recognizing the societal value of *Bt* effectiveness, EPA has required manufacturers of *Bt* crops to have insect resistance plans that include a requirement that growers plant an area of non-*Bt* corn or cotton to provide a refuge for susceptible pests[10] (EPA 1998; EPA 2001; Berwald, Matten et al. 2006). Planting a refuge is expected to dilute resistance by allowing mating between pests that may be highly resistant to *Bt* with those that are susceptible. In addition, EPA has required that the seed companies educate growers, have a compliance assurance program and an annual resistance monitoring program, and develop a remedial plan in case resistance is identified (EPA 2001). This is the first instance in which refuge areas have been required by regulation in the United States (Livingston, Carlson et al. 2000).

EPA's resistance management plan has been found to be effective in delaying the emergence of resistance to *Bt* crops and thus far appears successful (Tabashnik, Dennehy et al. 2005). It is interesting that EPA regulations regarding *Bt* are the first from any U.S. agency that treat pest susceptibility as a public good (Livingston et al. 2000), even though resistance issues arose with more traditional pesticides as well.[11] To date,

9 Critics of the legislation have reservations about its provisions to shield the new agency from public Freedom of Information Act requests and exempt it from longstanding and widely applicable laws on open records and public meetings.

10 The refuge requirement for *Bt* cotton has been in place since 1995, and for *Bt* corn since 1998.

11 It is interesting that transgenics triggered policy action but traditional pesticides did not. In both cases, an externality is present: any farmer applying a pesticide is helping to create a resistant pest population that can affect other farmers. The Pesticide Program Dialogue committee in 1996 recommended to EPA that protection of the susceptibility of *Bt* was in the "public good." In response to a lawsuit filed by Greenpeace in 1998, EPA recognized the higher selection intensity posed by transgenic *Bt* plants (since unlike conventional pesticides, a plant-incorporated protectant is always in the environment) and originally was concerned about the protection of microbial pesticides used in organic agriculture. The agency later expanded its concern for all *Bt* pesticides (plant-

there have been no major challenges to EPA's authority to regulate for pest resistance to *Bt*. This might indicate that in the interests of society, FDA could similarly regulate use of antibiotics or the conditions under which they are used.

In theory, FDA has sufficient power under current law to regulate for drug resistance in the interests of patient safety as proactively as EPA has regulated the planting of *Bt* crops. Current law permits FDA to grant conditional registrations that can be periodically evaluated to ensure that the registrant is meeting FDA's requirements for ensuring patient safety by minimizing the likelihood of resistance. However, FDA has not exercised this type of power and has not indicated a willingness to withdraw a drug approval because of emerging resistance to it.[12]

The nature of a regulatory solution

The basic framework for government action on antibiotics is clearly spelled out in the Antimicrobial Resistance Action Plan formulated by ITFAR.[13] The plan offers steps to changing incentives for both appropriate prescribing and better use of diagnostics to reduce the need for antibiotics. It specifically calls for actions to "identify economic and other barriers in the health care system (e.g., reimbursement policies by third-party payers, managed care practices, cost considerations, empiric treatment recommendations, etc.) to diagnostic testing that promotes appropriate use of antimicrobials" and "develop recommendations that remove disincentives or promote incentives to such testing." It also recognizes that "manufacturers are concerned that appropriate use policies may limit sales and profits" and calls for ways to "identify financial and/or other incentives or investments to promote the development and/or appropriate use of priority antimicrobial resistance products, such as novel compounds and approaches, for human and veterinary medicine for which market incentives are inadequate." Finally, it calls for a consideration of government's role in new drug discovery, especially where market incentives are limited.

Although based on a sound plan, current government response to the problem of antibiotic resistance has been hampered by important constraints. First, no single agency

incorporated protectants and microbial pesticides). The agency also recognized that *Bt* crops had the potential to displace higher-risk conventional chemical pesticides, and that there was strong public interest to maintain the environmental benefits of lower conventional pesticide use through effective management of *Bt* resistance.

12 The real reason may be a deep cultural difference between medical practice and agriculture. Looking over the shoulders of farmers to ensure that they undertake specific actions that are in the public interest, even if these involve a risk to the farmer's crop, is generally considered acceptable, whereas regulating a doctor's decisions on how to treat an individual patient (even if these actions involve risks to health of others) is not.

13 http://www.cdc.gov/drugresistance/actionplan/.

is charged with responsibility for antibiotic effectiveness. Although the ITFAR plan calls on CDC, FDA, and NIH to coordinate their activities, the agencies' representatives on ITFAR still have to make the case for doing something about antibiotics within their own organizations. Many actions, such as spending more on antibiotic resistance surveillance or basic science to support discovery of new antibiotics, compete with other priorities for staff time, funding, and attention. In other words, just the mandate to CDC, FDA, and NIH to take action to manage drug resistance does not necessarily give them incentive to make large changes and deviate from current structures. A review of ITFAR's goals and achievements over its five years of activity shows that many of the more easily attainable goals have already been reached, but the more difficult steps will require far more commitment and resources. For instance, creating a separate department within FDA to deal with antibiotics may require congressional authorization.

It may be illustrative to look at a model of action on federal management of fisheries. The Magnuson-Stevens Fishery Conservation and Management Act of 1976 declared Congress's interests in "the fish off the coasts of the United States … [that] constitute valuable and renewable natural resources." The act, which recognizes the economic and food-related importance of fish to the country, called for measures to protect the nation's fisheries and fish habitats through investments in fisheries development, data monitoring systems, fisheries management plans to "achieve and maintain, on a continuing basis, the optimum yield from each fishery," and federal permits, licenses, and other methods.[14] The Magnuson-Stevens Act is by no means a model for managing all resources, and this discussion is meant only to draw attention to the need for comprehensive legislation to consider antibiotics as a valuable national resource.[15] Moreover, it may be helpful to learn from both the successes and the failures of this earlier effort to manage a common property resource.

Comprehensive legislation to protect antibiotic effectiveness at the federal level would have three important advantages. First, it would recognize a vital national interest in the effectiveness of antibiotics that would signal to federal agencies the legislature's recognition of the importance of this problem. This is crucial because a mandate may not give the agencies sufficient reason to act (although the *Bt* example is one where that did happen); separate mechanisms

14 The Magnuson-Stevens Act was originally motivated by resentment over the presence of foreign fishing fleets off the U.S. coast as much as by concern over depleted fish stocks.

15 Although several revisions to the act have improved its performance, and the history of U.S. national fisheries is not a success by any standards, it is likely that the situation would have been substantially worse in the absence of the Magnuson-Stevens Act.

may be necessary. For example, the Magnuson-Stevens Act requires fisheries managers to identify and mitigate adverse impacts of fishing activity on essential fish habitat. Similarly, FDA could identify and mitigate actions that have an adverse impact on drug effectiveness. FDA's 2000 ban on selling fluoroquinolones for poultry can be seen as a precedent (Box 5.1), but this action fell well within FDA's role in protecting patient safety. In a hypothetical situation where the widespread use of one fluoroquinolone in human medicine is responsible for an increased likelihood of resistance to the entire class of quinolones, FDA's willingness to act is less clear.

Second, legislation specifically addressing the problem of antibiotic resistance could provide funding for programs to help conserve the effectiveness of existing drugs and support investments in new drugs. Work to prolong drug effectiveness must compete with other public health and biomedical priorities, and a separate line of funding that would pay for surveillance of resistance in hospitals and communities would help both public health officials and pharmaceutical firms in determining the need for new drugs. CDC, NIH, and FDA need funding for proactive measures to manage drug effectiveness as well.

Third, legislation would tie together actions to manage antibiotic effectiveness and those to improve the supply of new antibiotics, recognizing the impact of demand-side measures on supplier incentives and vice versa. Despite the advantages of the current regulatory structure, which links to other public health functions (such as CDC's role in responding to disease outbreaks), a coordinating body that bridges the mandates of existing institutions and reports directly to the secretary of Health and Human Services may be necessary.

CONCLUSIONS

The antibiotic resistance problem involves a common property resource—antibiotic effectiveness—that is likely being overexploited. Since resistant strains generated in one state can affect other states, federal action is appropriate. Federal agencies, most notably CDC and FDA, may have a mandate sufficient to undertake many of the actions needed to respond to the threat of resistance. The problem, however, is that they have weak incentives to do so and other priorities. Moreover, some remedies—such as giving pharmaceutical companies incentives to invest in new classes of antibiotics and relaxing antitrust or expanding patent scope to give them incentives to care about resistance—exceed the agencies' current mandates and would require action by Congress.

This report offers many specific policy ideas (Chapters 3, 4, 6, and 7). Pulling them all together into a coordinated response at the federal level may require new, comprehensive legislation specifically addressing antibiotic resistance. The problem is conserving a national resource, and piecemeal remedies, such as bills that create incentives for pharmaceutical companies (like the proposed Bioshield II legislation) or reduce inappropriate antibiotic use in livestock, may not be adequate.

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