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COMMENTARY

Eight More Ways To Deal with Antibiotic Resistance

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The fight against antibiotic resistance must be strengthened. We propose actions that U.S. government agencies and private sector entities can take to build a more comprehensive effort. These actions can increase the viability of investing in new antibiotics, ensure the quality and stewardship of all antibiotics, and make responses to emerging resistance more informed. Success requires the thoughtful exercise of federal authority and a firm commitment to share data and reward developers for the value generated with new, life-saving antibiotics.

There is an increasing and warranted sense of urgency to reverse the public health problem of antibiotic-resistant infections. Antibiotic-resistant infections are becoming more frequent culprits in treatment failures and are escalating health care costs. For 2013, the Centers for Disease Control and Prevention (CDC) estimated that in the United States alone, more than 2 million people were impacted by antibiotic-resistant infections, with at least 23,000 resulting deaths (1). These statistics are both likely underestimates and are limited to a small segment of the global population that is exposed to antibiotic-resistant bacteria. Three prominent experts in the field, Bartlett, Spellberg, and Gilbert, proposed "8 Ways to Deal with Antibiotic Resistance" (2), recommending goals for the health care and pharmaceutical development communities. These goals included diligence in the appropriate use of antibiotics (stewardship), more effective infection control, development of medical diagnostics to prevent inappropriate antibiotic therapy, and stimulation of renewed development of new antibiotics.

To reverse the regression to medicine without effective antibiotics, there must be concerted efforts to attack the problem from all angles and by many more parties. The actions must combat the spread of antibiotic resistance, reinvigorate the development of new antibiotics, and prolong the effectiveness of current and new antibiotic therapies. Therefore, we offer eight additional actions that the U.S. government and the private sector can take to combat antibiotic resistance.

1. Reduce clinical trial risk and uncertainty. The U.S. Food and Drug Administration (FDA) can significantly reduce the risk and uncertainty that discourages drug developers from pursuing new antibiotics by applying their unique access to data. A large hurdle in the approval of new antibiotics is the determination of just how great the clinical effect must be. The availability of robust and uniform historical controls to measure treatment effects against would greatly increase the feasibility of completing trial enrollment and remove some of the uncertainty that drug developers face in establishing endpoints. The FDA has accumulated numerous and varied data sets on clinical outcomes of infections under different treatment scenarios, including those with pharmacometric data. These data are available to drug developers only in fragmented, often proprietary records. The FDA should make these data useful to current drug development efforts by conducting and publishing a meta-analysis deriving historical control outcomes of different infections and under different conditions.

The FDA should continue to build on the progress it has made in the last few years toward using this analysis to establish clear, feasible, and uniform expectations of clinical effectiveness across the field of antibiotic indications. While likely to be imperfect, definition provided by a wide-reaching base of historical control data would have three important benefits. It would significantly reduce the uncertainty antibiotic developers face in trying to establish primary outcome expectations in clinical trials to meet regulatory acceptance. It will also increase the feasibility of completing trial enrollment. Acceptable historical controls will allow direction of all enrollable patients to investigational therapy. In the many cases of studies reliant on a limited enrollable population, this could make the difference between a study being feasible or not. For instance, use of a historical control could enable achievement of full enrollment in half the time that would otherwise be taken in a 1:1 investigational-to-comparator design.

Finally, use of historical controls will benefit patients by making investigational therapy accessible. In the current environment of failing conventional therapies, the opportunity to shrink comparator groups addresses a perplexing dilemma. The very urgency of developing new antibiotics stems from the growing number of intractable infections. By definition enrollable patients are most likely to fail conventional treatment. We have experienced the struggle of working through trial design where the integrity of the comparator arm is pitted against the risk of dooming patients who fail conventional therapy to having no treatment options. Once in the comparator arm of a study, patients are not readily transferred to the investigational therapy, even though it may be their only prospect for appropriate therapy. In fact, even regulators admit that an internally controlled study on a limited enrollable population is not feasible and in Europe have recognized historical controls as an acceptable solution (3). Measuring success of an experimental therapy against historical control data should be

Published ahead of print 27 May 2014

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doi:10.1128/AAC.02623-14

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given as much opportunity as possible to replace dependence on a conventional therapy-based comparator arm.

2. Boost market value for not feeding animals antibiotics. The U.S. Department of Agriculture (USDA) can catalyze market forces that will reduce the prolific agricultural use of antibiotics. The USDA has instituted certification of consumer products to set standards specific to industry practices and enable these to be recognized by consumers. Certifications such as "USDA Prime" for beef products (4) and "Organic" and "Biobased" on a wide range of commodities (5, 6) have as a side effect created labels with market value. The USDA should exercise this certification authority and create a "No Feed-Antibiotics" label to provide consumers with the same ability to discriminate food products that have been produced without growth-promoting antibiotics. Antibiotic use in agriculture is recognized as a contributor to increasing antibiotic resistance (7). Public awareness of this problem is sufficient to strengthen market incentives against the still prolific use of antibiotics in agriculture when combined with a widely recognized certification. This, and the next proposed action, will have incremental effects in reducing antibiotic use for animal growth promotion—the next best alternative to a ban such as Europe's, which has been unachievable in the U.S.

3. Strengthen regulation of farm feeding of antibiotics. The U.S. Environmental Protection Agency (EPA) can require manufacturers of antibiotics for agricultural use to generate data on the public health and environmental consequences of this use and can set limits on antibiotic use based on these data. The EPA has a long history of exercising its authority under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (8) to regulate residues from antimicrobial fungicides that accumulate in agricultural products and are released into the environment from farming. FIFRA requires pesticide manufacturers to register their products with the EPA before they can be marketed for agricultural use. The EPA should explore requiring FIFRA registration of antibiotics used in food animal production. The data requirements for registration will help to focus and support the restricted use that is important for deterring selection of antibiotic resistance in the food supply, as well as in the environment due to farm antibiotic effluents. Registration under FIFRA requires the generation of data on concerns such as "environmental fate" and dietary and nondietary hazards to humans. Furthermore, registrations granted under FIFRA stipulate the limitations and conditions under which registered chemicals can legally be used.

The prevailing opinion in the scientific community is that antibiotic use in agriculture contributes to the appearance of resistance in clinical settings and that antibiotic use for animal growth promotion is an unacceptable squandering of the finite lifespan of antibiotic efficacy. A large body of citations gathered by the Pew Campaign on Human Health and Industrial Farming (9) forms a hefty indictment of this kind of antibiotic use, although many of the references are either case reports or reviews/committee reports. Recent research reveals associations between resistance in agricultural, environmental, and community settings (10) and even indicates movement of antibiotic resistance through the food supply into the community (11, 12). At the same time, there are new data on *Salmonella* indicating that distinct populations of antibiotic-resistant bacteria can exist largely segregated in human and farm animal populations (13).

In December 2013, the FDA released Guidance for Industry number 213, which seems unlikely to reduce the impact of using antibiotics as growth promoters in farm animal production on the development of resistance. Although almost all of the producers of antibiotics affected by the guidance signaled their intent to request withdrawal of their approvals for feed use (14), many withdrawal requests are stated to be because the, "products are no longer manufactured or marketed" (15). The guidance focuses on eliminating the growth-promoting use of just "medically important" antibiotics (16). This does not appear to be removing antibiotics from use that are currently marketed and used for animal growth promotion. Further, it will not close the gate on collateral selection for resistance against medically important antibiotics, when genetically linked resistance elements to other antibiotics remain under selection.

While most of the scientific community (these authors included) strongly opposes continued use of antibiotics for animal growth promotion, a ban such as that in Europe has not been achievable. More extensive data on antibiotic-resistant zoonoses and regulation of antibiotic use in animal husbandry based on data that FIFRA could require are needed. An example of the much-needed data that could come from closer study is information on the degree to which clinically relevant antibiotic resistance genes may hitchhike on mobile genetic elements with the one(s) under selection. Mobile genetic elements are well known to simultaneously carry multiple resistance genes against widely different antibiotics (17).

The problem of antibiotic use in agriculture accelerating the development of resistance in human infections now looks more likely to be tackled by the EPA than by the FDA. The interpretation of EPA's FIFRA authority has been extended so far as to be applied to insecticidal proteins in genetically engineered plants. Given the negative public health consequences of improper and excessive agricultural use of antibiotics, FIFRA should reasonably be extended into this arena.

4. Unify U.S. government efforts. The president of the United States can require coordination of efforts by the various federal agencies that have a role in combatting antibiotic resistance. An ongoing U.S. government working group, the Interagency Taskforce for Antimicrobial Resistance (ITFAR), has been working to communicate federal efforts related to combatting antibiotic resistance (18). The ITFAR has to date succeeded in sharing information among various agencies from the U.S. Department of Health and Human Services (CDC, FDA, National Institutes of Health [NIH], the Centers for Medicare and Medicaid Services, the Biomedical Advanced Research and Development Authority, and others), the U.S. Departments of Agriculture, Defense, and Veterans Affairs, and the EPA. The ITFAR should be given more authority so that it not only provides participating agencies and the public visibility into what different agencies are doing to combat antibiotic resistance but also can require agencies to make commitments as to future actions and prioritization of activities to combat antibiotic resistance. As is clear from the work of this and many other multi-agency task forces, the individual agencies will not move from contributing to a discussion to complying with direction until there is an executive order. The President of the United States should empower ITFAR to harmonize and focus U.S. federal agencies' efforts at combatting antibiotic resistance.

5. Incentivize early sharing of data. Publishers of peer-reviewed scientific journals can remove disincentives to sharing information prior to publication when there are public health threats such as emerging antibiotic resistance. Typically, research-

ers closely guard data about new discoveries until they amass enough data and analysis for publication. In the case of the infamous NDM-1 antibiotic resistance gene, almost a year intervened between its discovery and the knowledge of its existence being made public (19). In the intervening time, the tools for detecting and controlling its spread remained undeveloped while it crept across various continents. Journal editors need to exercise their authority over the publication process and incentivize the early release of data that are critical to public health efforts like understanding and containing antibiotic resistance. Part of the delay in the release of information results from the publication process itself—in the case of NDM-1, the original article was submitted in June 2009 and only published in December 2009. Rapid publication and open online access are existing mechanisms for accelerating the dissemination of information, but these may be insufficient to overcome long review times and the insistence of journal editors that information in manuscripts that have not completed peer review be left uncommunicated ahead of publication. While other interests such as intellectual property also compete with rapid sharing of data, protecting the currency of publication for authors who share early should have a positive impact.

Journals could improve the situation by establishing policies providing for expedited review of appropriate submissions or allowing prereview publication based on a preliminary review by appropriate editors. After publication of a prereview article, priority could then be given to bringing forward a more polished version as a final publication. The disclosure of the data for the benefit of public health prior to it appearing in a polished manuscript would no longer be penalized with diminished chances of publication or risk of others racing ahead with a preemptive publication analyzing the disclosed data.

6. Assure the quality of generic antibiotics. The FDA can hold manufacturers of generic antibiotics to the same standards of drug potency as the name-brand manufacturers. Drug regulators allow generic drugs to enter the market with relative leniency applied to how much they must perform like their name-brand progenitors. This feature of likeness is termed bioequivalence. The FDA's guidance to industry for generic antibiotics recommends exposures within a 90% confidence interval of the branded version. This threshold is not assured, as the vast majority of the FDA guidance documents for specific generic antibiotics are draft and nonbinding (20). Furthermore, since the recommended studies make no specifications for pharmacokinetic (PK) properties, studies with very limited PK sampling in terms of population size and time points could easily overlook inadequate drug exposure levels. This level of flexibility is not appropriate for antibiotic dosing. Underdosing antibiotics is one way to accelerate resistance development. Regulators need to more earnestly gather data on cases where generic antibiotics perform less effectively than name-brand versions (studies on this topic vary widely) and should use this evidence to establish a more appropriately stringent bioequivalence requirement for generic antibiotics. This will raise the quality of the generic antibiotics frequently used to treat infections and reduce the chances of inadequate dosing. It will be of further benefit to enforce similar quality standards on veterinary antibiotics. Rigorous quality standards in the U.S. market can serve as a catalyst for improvements globally.

7. Level the playing field between new and old antibiotics. The FDA can apply the same standards to antibiotics seeking new approvals as to those that are currently generic and so alleviate this particular disincentive for antibiotic development. Antibiotics currently on the market and in generic form ride on approvals granted with much less stringent requirements than are imposed upon antibiotics seeking regulatory approval today. The FDA should equalize the labeling standards for generics and name-brand antibiotics, such that a new antibiotic does not require more information on its label than is required of a generic currently in use for the same indication. Two new movements by the FDA signal an encouraging change in this direction: one would allow generic manufacturers to change their safety labeling (21), and the second would allow label changes that incorporate antibiotic susceptibility breakpoints supported by modern PK data (22). A more inclusive approach to label changes removes the conundrum of having to work with a brand-name manufacturer when none exists and provides more speed and flexibility to get safety labeling out to physicians and patients. Regular review of the antibiotic susceptibility breakpoints for generic antibiotics must be carried out. Having modern breakpoint data on both old and new antibiotics will better inform regulatory decisions about the relative risk and benefit of a new approval, as well as guide better treatment decisions in the clinic. Asymmetric standards should no longer place new antibiotics at a disadvantage against the failing old antibiotics that we require replacements for.

8. Assure value-based pricing of new antibiotics. Public and private payers of health care costs (e.g., Medicare and insurance companies) can incentivize developers of new antibiotics by promising them a share of the savings that will be realized with effective treatments. Antibiotic-resistant infections in the United States can be blamed for millions of illnesses and thousands of deaths annually. Not only is this a dreadful burden of morbidity and mortality, but with estimated additional per-patient costs of $18, 000 to $29,000 based on a recent study in the United States (23), it is a hefty direct financial burden on the health care system. An earlier study published in 2003 found methicillin-resistant *Staphylococcus aureus* (MRSA) infections to increase the cost of hospitalizing patients by $13,000 compared to the costs of infections with susceptible *S. aureus* strains (24), suggesting that the cost has been growing. New antibiotics that overcome existing resistance clearly have the capacity to save lives and resources that would otherwise be lost to untreatable infections. To date, there has not been a scheme to reward antibiotic developers for the value that new drugs of this class will accrue to the health care system. Value-based pricing has been proposed (25) as a way to recognize this value and pay pharmaceutical developers proportionally to health care costs that are saved when an otherwise untreatable infection is rendered treatable. Public and private health care payers should develop and commit to a scheme for value-based pricing of new antibiotics. In public discussions, payers have signaled a willingness to entertain paying a higher cost for life-saving antibiotics (26). A commitment to a specific payment scheme is now needed to reduce valuation uncertainty, which is a major deterrent. If developers can anticipate being paid a portion of the savings that their products create in the health care system, antibiotic development will become a more viable investment.

Antibiotic resistance is a serious public health problem that is continuing to grow and outpace the development of new, effective antibiotics. This problem will only be brought under control through a holistic and comprehensive set of actions involving many responsible parties. We offer specific actions that U.S. government agencies and private sector entities can

take to improve antibiotic stewardship and revitalize antibiotic development. Some of these actions represent the next best options to actions being taken in other parts of the world, such as the EU ban on use of antibiotics to promote animal growth. Others, like equalizing the requirements for generic and new antibiotics and value-based pricing, can blaze a trail for others to follow towards improved sustainability of antibiotics.

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