



## **Comments for the Public Health Action Plan to Combat Antimicrobial Resistance**

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### *Overall comments*

The Public Health Action Plan to Combat Antimicrobial Resistance has mapped a strong coordinated effort for addressing the problem of drug resistance, including various federal agencies, interstate networks, and stakeholders across human and veterinary medicine, agriculture, basic and applied sciences, among others. On behalf of ReAct—Action on Antibiotic Resistance ([www.reactgroup.org](http://www.reactgroup.org)), a global network dedicated to combating antibiotic resistance, we welcome the opportunity to provide public comment and feedback on this important effort. Paralleling some of the key objectives of the Public Health Action Plan, ReAct's work spans from developing new business models for antibiotic innovation to training health workers how to improve rational use of antibiotics.

For the Public Health Action Plan, it is important that it reflect in its entirety the shared global challenge of antimicrobial resistance (AMR). In an era of globalization, the spread of drug-resistant pathogens occurs transnationally. If global access to appropriate treatments and strategies fails to be realized, then the efforts of the U.S. and other countries to combat the inherently global problem of AMR will be limited in effectiveness and worldwide health inequities would increase.

Under Point 10 of the Public Health Action Plan, the call for international harmonization holds great promise for maximizing the impact of each area of the Public Health Action Plan. With respect to the use of antibiotics for livestock animals, for example, several countries in Europe could provide models for phasing out certain uses of antibiotics for which the harms of increased AMR may outweigh any animal health or economic benefits.<sup>1</sup> For the Public Health Action Plan's goals for surveillance, prevention, and control of the spread of drug resistance, the uniformity of definitions and integration of surveillance systems across the board could serve to minimize the spread of drug resistant bacteria. In the case of transnational spread of New Delhi metallo- $\beta$ -lactamase-1 (NDM-1), had surveillance among hospitals engaged in medical tourism been coordinated from country to country, the spread of NDM-1 may have been identified sooner and the new cases of NDM-1 contained.<sup>2</sup> Hospitals engaged in medical tourism as beacons of quality in their healthcare systems have a special responsibility and opportunity to show leadership in these antibiotic stewardship efforts.

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<sup>1</sup> Silbergeld E, Davis M, Leibler J, Peterson A. "One reservoir: redefining the community origins of antimicrobial-resistant infections." *Med Clin N Am* 92 (2008) 1391–1407

<sup>2</sup> So A, Furlong M, Heddini A. "Globalisation and antibiotic resistance." *BMJ* 2010; 341:c5116

## *Surveillance*

As the U.S. monitors drug resistance, cases of infection, and antimicrobial use, it is important that surveillance not be an end to itself, but rather serves as a means to improved stewardship of antibiotics and other health technologies and knowledge. For example, several maps now illustrate the regional concentration of drug resistance or how diseases spread geographically.<sup>3</sup> We recommend that such surveillance data feed into a system of continuous quality improvement and contribute as a key actionable goal in the \$1 billion effort that the US Department of Health and Human Services has just announced to reduce medical errors in partnership with insurers, business leaders, hospitals and patient advocacy groups. As the slogan in the Institute for Healthcare Improvement's 100,000 Lives Campaign reminds us, "Some is not a number. Soon is not a time."<sup>4</sup> Measurable goal posts are needed. To make these goals actionable, it is important that surveillance of resistant organisms go hand in hand with systems to track antimicrobial use. Burden of AMR will also require economic data of the resulting costs incurred, from prolonged hospitalizations to preventable deaths.

## *Prevention and Control*

As the U.S. develops its approach to minimize the impact of AMR, it is important that these health technologies and strategies be tiered appropriately for the different levels of resource available at target settings. For example, hospitals, community clinics and public schools each differ greatly in the staffing and infection control measures that they can bring to bear on monitoring and controlling the spread of drug-resistant pathogens. Tools in some settings must be lower cost and demand less time and training of staff. Such approaches may also have useful spillover benefits when cross-applied to similarly resourced tiers of health care systems in low- and middle-income countries. Importantly, the success of preventing and controlling AMR depends on a global effort, inclusive of all countries.

Building the experience of the Institute for Healthcare Improvement, the US Public Health Action Plan might develop its own Breakthrough Series Collaborative on AMR. Such a strategy would (1) connect teams of health care workers with clinical science and application experts at "Learning Sessions," (2) create a community of innovators and implementers that are working together in a stepwise process towards these milestones, and (3) provide the impetus and "Action Periods" for groups to return to their clinics and hospitals to execute these plans.<sup>5</sup> IHI's model alternated brief Learning Sessions with Action Periods in order to provide teams the chance to reflect on their implementation strategy's effectiveness and then improve it during the next Action Period. Combined with goals such as those laid out in the IHI's 100,000 Lives Campaign, measurable gains towards AMR might be achieved.

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<sup>3</sup> These include the Center for Disease Dynamics, Economics & Policy's ResistanceMap taking U.S. inpatient drug resistant infection data from the Surveillance Network Database – USA(TSN) or the Center for Global Development's international mapping of certain types of drug resistance.

<sup>4</sup> Institute for Healthcare Improvement [Website]. "Overview of 100,000 Lives Campaign." Accessed April 12, 2011. <http://www.ihc.org/IHI/Programs/Campaign/100kCampaignOverviewArchive.htm>

<sup>5</sup> Institute for Healthcare Improvement. "The Breakthrough Series: IHI's Collaborative Model for Achieving Breakthrough Improvement" [Online White Paper.] 2003. <http://www.ihc.org/NR/rdonlyres/BCA88D8F-35EE-4251-BB93-E2252619A06D/0/IHIBreakthroughSerieswhitepaper2003.pdf>

Using an approach similar to Ashoka Changemaker’s competitions and the “Saving Lives at Birth: A Grand Challenge for Development” competition (cosponsored by USAID, the Gates Foundation, Grand Challenges Canada, the Government of Norway, and the World Bank), we would also encourage the Public Health Action Plan to create a community of innovators to develop breakthrough interventions, in clinical practice, technology and policy, by supporting seed and scale-up funding for the challenge.<sup>6</sup> A crowdsourcing model importantly invites insight and innovation from those on the frontline of care who otherwise may not be heard. Prizes can not only help incentivize the development of such ideas, but also nurture their scale up.

In addition to the Public Health Action Plan’s goals of developing alternatives to antimicrobial treatments for food and educating food producers and handlers, we recommend that the Public Health Action Plan include a goal to develop a point-of-use diagnostic to reveal resistant, food-borne pathogens, with the results visible to policymakers and the public. Because of the public value of such a diagnostic, the NIH National Center for Advancing Translational Sciences (NCATS) may be the most appropriate player to develop the diagnostic.

In conceiving of innovative strategies to combat antimicrobial resistance, we might also draw insights from a deeper understanding of the ecology between humans and microbes. The IOM workshop, "Ending the War Metaphor: The Changing Agenda for Unraveling the Host-Microbe Relationship," highlights how "a convergence of biological, environmental, sociopolitical, and ecological factors...can be seen to influence the host-microbe relationships that lie at the core of disease emergence." Such a paradigm shift may pave the way for approaches, such as probiotics where the use of live microorganisms may offer salutary benefits on the host. A ReAct-supported project, Microbiana ([www.microbiana.org](http://www.microbiana.org)), has recently brought together scientists, artists and others across disciplines to discover new ways of understanding these relationships. More work along these lines might open a new front in the campaign to curb antimicrobial resistance.

### *Research and Product Development*

In order to improve the R&D pipeline for antimicrobials, upstream, the U.S. should consider the use of target product profiles (TPPs), defined by the FDA as a “summary of a drug development program ... [providing a] format for discussions between a sponsor and the FDA that can be used throughout the drug development process.”<sup>7</sup> TPPs can signal R&D priorities to researchers and companies, provide a level of certainty to the regulatory process for a new drug, and ensure that economic incentives align with public health needs.

For those TPPs for which there is insufficient market demand to begin the research process, we recommend that the Public Health Action Plan include coordination with efforts like NCATS, Therapeutics for Rare and Neglected Diseases (TRND), the National Center for

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<sup>6</sup> Saving Lives at Birth [website]. “How to Apply.” Accessed April 13, 2001. <http://www.savinglivesatbirth.net/apply>

<sup>7</sup> Center for Drug Evaluation and Research, 2007. Guidance for Industry and Review Staff: Target Product Profile—a Strategic Development Process Tool. U.S. Department of Health and Human Services, Food and Drug Administration, Washington, D.C.

Chemical Genomics (NCCG), or Rapid Access to Interventional Development (RAID), to help bridge the gaps upstream in R&D. Their important contributions might lower the barriers to entry for promising R&D efforts, particularly smaller firms and academic research institutions, as well as increase the pursuit of riskier drug candidates in a faltering antimicrobial R&D pipeline.

For upstream innovations to R&D, we also recommend that surveillance systems and the development of novel diagnostics be organized in a way that might help facilitate the more rapid recruitment of patients for clinical trials testing novel antibiotics. Such a system has promise to lower significantly the costs and time associated with clinical trial testing of breakthrough therapies.

We understand the importance of developing effective incentives for firms to pursue the development of technologies, particularly novel classes of antibiotics, that might help combat growing drug resistance. The Public Health Action Plan suggests looking at how R&D incentives like those provided under the Orphan Drug Act (ODA) might be repurposed to improve R&D into new antibiotics. However, we would caution against efforts, such as patent extension, data exclusivity and market exclusivity, that fail to delink drug company revenues from volume-based sales. Such approaches not only do not serve consumer interests here and abroad, but also are at odds with efforts to improve rational use. Rationing by price is irrational. As gout patients reliant on colchicine and pregnant women taking 17 alpha-hydroxyprogesterone caproate (17OHP) to prevent preterm births have painfully learned, such approaches have resulted in exorbitant prices, not justified by the R&D investments. Of note, for all orphan new molecular entities (NMEs) approved between 1983 and 2007, only one out of ten NMEs benefited from taking advantage of market exclusivity.<sup>8</sup> Rather incentives need to be designed to be targeted, derisk key bottlenecks upstream in the R&D pipeline, and in these difficult economic times, insist on fair returns to the public from taxpayer investments.<sup>9</sup>

Finally, we urge the Public Health Action Plan to Combat Antimicrobial Resistance to identify concrete ways to build the momentum to tackle these issues through inter-governmental fora, from the WHO's World Alliance for Patient Safety to the Transatlantic Task Force on Antimicrobial Resistance (TATFAR). Along these lines, we also share our input to TATFAR as appendix to these inputs. The U.S. Public Health Action Plan must stand as one with other countries if we are to make gains against this challenge in a globalizing world.

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<sup>8</sup> Seoane-Vazquez E, Rodriguez-Monguio R, Szeinbach SL, Visaria J. "Incentives for orphan drug research and development in the United States." *Orphanet J Rare Dis.* 2008 Dec 16;3:33.

<sup>9</sup> So AD, Gupta N, Brahmachari SK, Chopra I, Munos B, Nathan C, Outtersson K, Paccaud JP, Payne DJ, Peeling RW, Spigelman M, Weigelt J. "Towards new business models for R&D for novel antibiotics." *Drug Resist. Updat.* (in press), doi:10.1016/j.drug.2011.01.006

## About ReAct

Founded in 2004 and operating as an international secretariat with its administration based in Uppsala University in Sweden, ReAct aims for profound change in awareness and action to manage the interacting social, political, ecological and technical forces that drive the rising rate of resistant human and animal infection and the rapid spread of resistance within and between communities and countries. ReAct addresses antibiotic resistance on a broad agenda driven by a strategic focus on the complex interaction of factors driving resistance. For example, ReAct both stimulates and/or coordinates activities to:

- Communicate the problem more effectively and mobilize widely for society's involvement and understanding;
- Make its health and societal impact more visible and measureable;
- Promote new ways of understanding the fundamental relationships, both beneficial and harmful among humans and microbes and its ecological dimension;
- Stimulate new public/private business models to solve the stalled research and development of needed new technology (diagnostics, preventatives and treatments) for bacterial disease; and
- Identify and cross-fertilize learning about successful initiatives to radically improve the effective use of antibiotics and stop their misuse in hospitals and the community.

For more information on ReAct, please visit [www.reactgroup.org](http://www.reactgroup.org).



## ReAct Comments for the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) – December 2010

### *Cooperation between the US and the EU*

As the concerns over trans-border spread of NDM-1 illustrate, cooperation between the US and the EU cannot limit its scope to bilateral efforts across the Atlantic to combat antibiotic resistance. Such a provincial approach would inevitably fall short. However, both the US and EU can work towards building a common platform for supporting global efforts to enhance novel antibiotic innovation through innovative financing for R&D, strengthening public health surveillance for tracking data, and building health system capabilities to encourage rational use and to tackle antibiotic resistance.

In so doing, these efforts should be ever mindful of the spillover impact on the global picture of antibiotic resistance. For example, supply chain interventions downstream can have ripple effects on producers and their non-therapeutic use of antibiotics as inputs into foods. Developing novel antibiotics—without attention to affordability—will contribute to irrational use and denied access, rationed by price. Applying extended data exclusivity as an incentive for antibiotic innovation mindlessly ignores what industry already has acknowledged and recognized at the recent Uppsala ReAct conference, that rewards have to separate the costs of R&D from the sales of the product.

ReAct recommends that TATFAR pursue the following objectives:

- Building on successful efforts to address antibiotic resistance at the national level, formulate policy recommendations to governments on key elements in programmatic approaches to manage antibiotic resistance;
- Developing approaches to incorporate surveillance data globally from sentinel sites that allow for timely and locally actionable feedback;
- Providing a framework for assessing and tracking the clinical and economic impact of antibiotic resistance in community and hospital-based delivery systems;
- Tapping into the signaling potential of monitoring news and activity on the Internet, but go further in tracking trends rather than just outbreaks and prospectively identifying findings that merit true rather than false alarm;
- Translating surveillance data on antibiotic resistance into metrics for priority setting (e.g., the value of investing in a new diagnostic technology might be measured in terms of numbers of treatments averted) and possibly the development of target product profiles for R&D innovation;
- Building upon models for pharmaceutical innovation, found for neglected (e.g., proprietary compound library access arrangements and product development partnerships) and rare diseases (e.g., programs like NIH TRND and RAID that bolster small firm and academic laboratory efforts to move promising leads to first-in-man trials) as well as growing efforts for collaborative, open innovation (e.g.,

- research consortia like the Structural Genomics Consortium or public-private efforts to share clinical trial data like the Coalition Against Major Diseases' database for Alzheimer's and neurodegenerative diseases) to lower the barriers to novel antibiotic innovation; and
- Encouraging governments to provide public funding for antibiotic R&D and to support the development of alternative funding models that delink the recouping of R&D costs from sales of the product, but rather conditioned on ensuring fair returns to the public, both through affordable pricing and rational use.

### *Looking beyond the EU and US: a global perspective*

If TATFAR can successfully lay the foundation for a global—and not just bilateral—effort to address the challenge of antibiotic resistance, it would be helpful if the Task Force might consider whether its mandate be extended under the current arrangement and/or whether there might be value in broadening participation to include other interested countries and regions. Reinvigorating and integrating efforts at the World Health Organization on antibiotic resistance would also be a worthwhile and complementary part of efforts going forward.

### *Further recommendations for TATFAR's three areas of focus*

#### *1. Appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities*

##### 1.A. Medical Communities

Rational therapeutic use for antibiotics is a cornerstone to conserving the effectiveness of existing antibiotics. Through regional dialogues in Asia, Africa and Latin America, we have come to realize the difficulties of suggesting a “one size fits all” tool kit of best practices for policy makers and healthcare providers to encourage rational use of antibiotics. We have to move beyond inventories of best practices and checklists. In putting forward such guidance, the Task Force might consider:

- Moving beyond checklist approaches to a more context-sensitive strategy where potential best practices recognize differences in local health systems, cultures and resource levels;
- Developing approaches to measure performance to combat antibiotic resistance and ensure greater accountability at different points in the healthcare system;
- Encouraging end-user innovation and the sharing of such innovative practices combat antibiotic resistance through an on-line collaborative competition, partnering with philanthropies, professional societies, insurers and other key stakeholders;
- Aligning economic incentives for rational use of antibiotics, both for providers and patients, through prescription, pricing, and reimbursement practices, again in a manner sensitive to the local context of health care delivery systems;
- Enabling effective feedback mechanisms that promote rational use of antibiotics and clinical management strategies that minimize patient risks and liability for “watchful waiting” by healthcare providers;
- Curbing marketing activities that promote wrongly the use of antibiotics; and

- Supporting policy implementation and health services research to address effectively these issues across a range of industrialized and developing country settings.

### 1.B. Veterinary Communities

The transmission of bacterial resistance from animals to humans has prompted concerns over appropriate therapeutic use of these drugs in animal husbandry and efforts to halt the non-therapeutic use of these drugs, particularly for growth promotion. Purchasers and consumers can influence upstream suppliers over their use of antibiotics by conditioning what inputs enter the supply chain. Further approaches to hold accountable the use of antibiotics for rational, therapeutic purposes deserve attention.

ReAct urges the Task Force to consider:

- Identifying effective strategies to control, without jeopardizing the effectiveness of antibiotics for human use, both zoonotic infections and animal diseases endemic in many systems of food animal production;
- Sharing and emulating successful efforts to both phase out certain antibiotic use in livestock, and restrict and track through prescriptions the veterinary use of antibiotics for appropriate therapeutic use;
- Examining the supply chain from farm to food outlet for potential intervention points to encourage better antibiotic use (e.g., rapid point-of-use diagnostics to detect food contaminated with pathogenic bacteria and resistant strains); and
- Developing the range of incentives and disincentives, including financial, which might be part of the broader set of measures to encourage better antibiotic use practices in animal husbandry.

### *2. Prevention of both healthcare- and community- associated drug- resistant infections*

Drug-resistant infections worsen health outcomes in both community and hospital settings. From the Institute for Healthcare Improvement's Five Million Lives Campaign to the World Alliance for Patient Safety's Hand Hygiene and Safe Surgery campaigns, various efforts can inform a potential strategy going forward. To move both healthcare accreditation organizations and healthcare institutions from standards to real stewardship, the Task Force might consider:

- Using a campaign-style approach with measurable goals to mobilize health care institutions and providers to target specific practices that might have the greatest return for infection control;
- Developing continuous quality improvement techniques, alongside guidelines, educational interventions and reporting and learning systems, that could be adapted to a range of community and hospital-based settings, including in resource-limited countries, to improve infection control and appropriate antibiotic use;
- Examining the potential for development and wider adoption of innovative health technologies that might minimize the emergence of antibiotic-resistant infections in the healthcare setting (e.g., medical instrumentation surfaces resistant to bacterial colonization);

- Aligning reimbursement incentives to encourage best practices for infection control; and
- Applying supply chain analysis to studying where and how to overcome Information blindspots, stockout problems, and other system-level failures that compound problems of antibiotic resistance.

### *3. Strategies for improving the pipeline of new antimicrobial drugs*

While conserving existing antibiotics is key, the dearth of novel antibiotics presents direct consequences. The EMEA-ECDC-ReAct analysis of the pipeline for antibiotics reveals not a single antibiotic with a new mechanism of action in development, and just two with possibly new targets that are active against Gram-negative infections. Reinvigorating this R&D pipeline is essential, but given the potential costs and tradeoffs in financing this over other strategies to address antibiotic resistance, the public investment must be made responsibly. This is not a call for throwing every financial incentive at the problem, but one of targeting strategically. Nor is the problem solely financial. There are significant scientific challenges to address. The preparatory work and productive discussions at the Swedish EU Presidency meeting on “Innovative Incentives for Effective Antibacterials” in Stockholm in September 2009 provides a useful starting point; and the more recent Uppsala ReAct conference on “The Global Need for Effective Antibiotics” a year later has further deepened the analysis of how to respond to these challenges.

Responding to this faltering pipeline for health technologies to combat antibiotic resistance, we urge the Task Force to consider:

- In allocating finite public resources for this challenge, that opportunities to develop diagnostics and/or vaccines where appropriate ought not be overshadowed or supplanted by a focus solely on antibacterial drug development. In fact, encouraging co-development of drugs and diagnostics also warrants attention;
- In defining target product profiles for antibacterial drug development, that the focus of R&D incentives be on antibacterial drugs with novel mechanisms of action, not "me too" additions;
- In rethinking the business model for bringing new health technologies to market, that approaches that delink the recouping of R&D costs from sales of products, thereby making products more affordable in low- and middle-income countries, be developed. Product development partnerships—existing or new—may be required to pilot or test out these approaches.
- In borrowing from efforts to accelerate innovation for treatments of neglected and rare diseases, that approaches to lower the barrier of scientific challenges also receive support, thereby enabling innovative small firms and academic institutions to participate in these efforts; and
- In considering fair returns on public investment, that a global perspective taking into account the importance of affordability and access in ensuring rational use, particularly in countries outside Europe and the US.